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A Pituitary Insulotropic Principle[1]

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IN A preliminary report (6) we showed that the same extract of anterior pituitary gland which is eventually diabetogenic in dogs quickly intensifies the hypoglycemia of human patients suffering from organic hyperinsulinism (pancreatic islet cell tumor); that the hypoglycemic effect of the extract is prompt and rapidly lost upon cessation of injections; and that the stimulus for increased production of insulin cannot be attributed to an intervening hyperglycemia since the latter never occurred. It was concluded that there exists in 'diabetogenic extracts' of anterior pituitary gland an insulotropic factor which exerts its effect directly upon the islands of Langerhans, and that this factor may be identical with that which initiates islet cell degeneration in some species. The details of our experiments are herein recorded.

METHODS

Human subjects

Two patients, one male and one female, suffering from severe and persistent spontaneous hypoglycemia resulting from chronic endogenous hyperinsulinism (excessive amounts of functioning islet tissue) were used as the subjects of this investigation.[2] Both patients satisfied all of the clinical and laboratory criteria necessary for the diagnosis of organic hyperinsulinism (7). In one case the diagnosis was subsequently proven at operation, at which time a pancreatic islet cell tumor was removed with a resulting complete cure of the entire disturbance. The other patient refused operation. Both had been having frequent periods of unconsciousness with blood sugar

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[2] For detailed case histories see appendix.

levels ranging between 12 mg. and 30 mg. per 100 cc. of blood.

Diet and blood sugar determinations

Since in organic hyperinsuli ism the average fasting blood sugar level is the most important single criterion of severity (while the patient is eating a constant diet and activity is minimal), a daily pre-breakfast blood sugar determination was done throughout the entire period of study. Serial glucose tolerance curves were obtained during various phases of the work. Blood sugar was determined by the Benedict method (1). A constant weighed diet containing 80 gm. of protein, 300 gm. of carbohydrate and maintenance calories was fed.[3]

Nitrogen determinations

Nitrogen balance studies were conducted in patient, *A. P.*, for 87 of the 92 days of study. Urinary nitrogen was done by the Kjeldahl method. Stool nitrogen was assumed to represent 10 per cent of the intake.

Preparation of extract

A crude, saline extract of fresh, frozen beef, anterior pituitary glands was prepared according to Young (30). Fractional precipitation produced a clear solution (to be the subject of a later report); 1) having a markedly diabetogenic effect in normal dogs; 2) capable of producing permanent diabetes in normal dogs by daily intravenous injections; and 3) producing no untoward reaction in dogs when given intravenously daily for over 200 days. All extracts used in the patients were first determined to be bacteriologically sterile and were administered subcutaneously. Chemical procedures, storage, and Berkfeldt filtration were carried out at temperatures below 4°C. Extracts more than seven days old were not used.

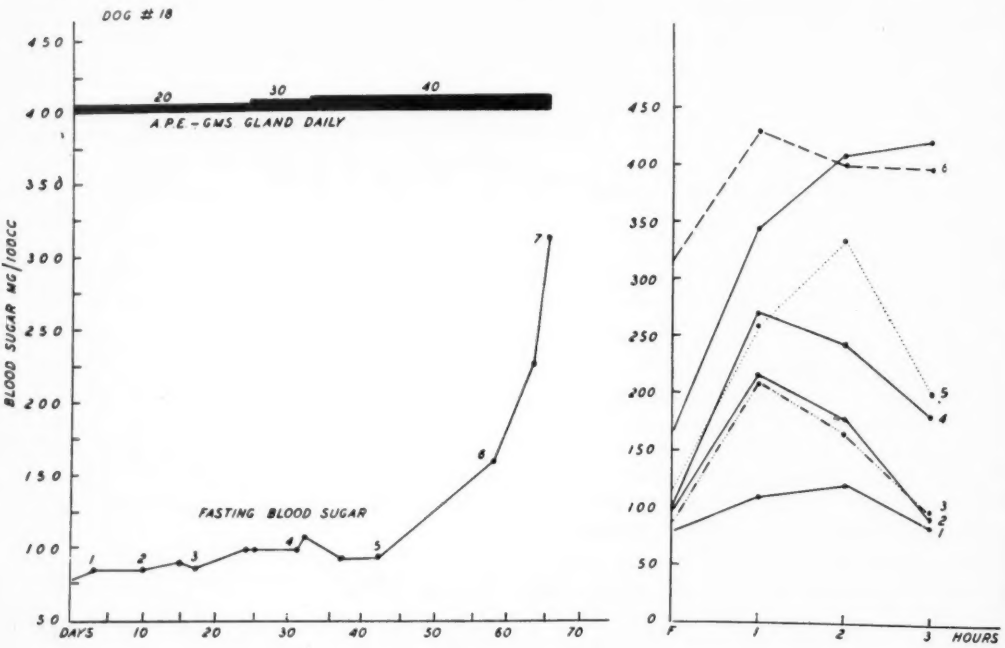


FIG. 1

Dog #18 (Fig. 1) is presented as an example of the response obtained in dogs to daily intravenous injections of the same extract as that used in the patients. This animal was

[3] In patient *A.P.* the following diet (P—50 gms. CHO —50 gms., cals. 1200) was fed for a short period in order to compare its effect on the fasting blood sugar level with that of the standard diet.

chosen as the example because the time required to produce an elevation of the fasting blood sugar level was somewhat longer than the average, and allowed time for serial glucose tolerance tests to indicate a "pre-diabetic" state.[4]

Note that between the 42nd and 60th day of injection, the fasting blood sugar rose to the level usually observed in the completely depancreatized dog; that when the normal fasting blood sugar level was finally 'broken through,' the subsequent rise was sharp and progressive. It is significant that long before the fasting blood sugar level began to rise, evidence of decreasing tolerance for carbohydrate was apparent from the serial glucose tolerance curves. It is thus clear that the extract employed is definitely diabetogenic when administered to dogs.

Figure 2 shows the results obtained in the first patient studied (*A. P.*, male, aged 27). *Periods I and II* contrast the effects on the fasting blood sugar level of a diet low in carbohydrate and protein with that obtained on an average normal diet. *During all subsequent periods* the diet eaten was identical with that ingested during Period II.

Period III. The daily injection of an amount of extract equivalent to ten grams of fresh anterior pituitary gland resulted in a precipitous fall of the fasting blood sugar level. The average is comparable to that obtained on the low carbohydrate diet.

Period IV. An abrupt rise of the level of the fasting blood sugar occurred when the extract was discontinued.

Period V. For the next 23 days the subject received daily injections of extract equivalent to 40 grams of fresh gland per day. Again a sharp fall of the fasting blood sugar level was obtained. There was some tendency for the level to rise in the latter half of the period (second half—av. 34 mg. per cent, first half —av. 29 mg. per cent).

Period VI. (Fig. 3). This three day 'rest period' is too short to place much significance on the average level of 42 mg. per cent. It is interesting, however, to note that the rise of the fasting blood sugar upon cessation of injections was not as acute as that observed upon cessation of the first series of injections (the transition from Period III to Period IV).

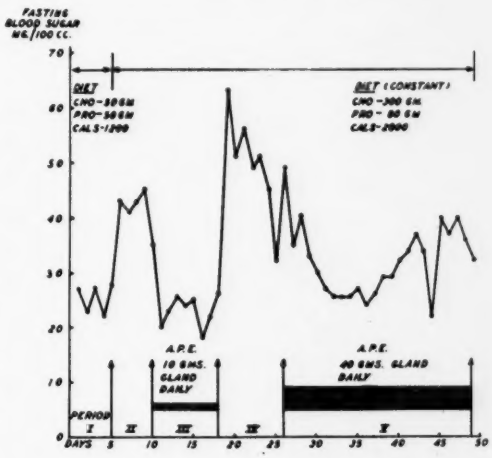


FIG. 2

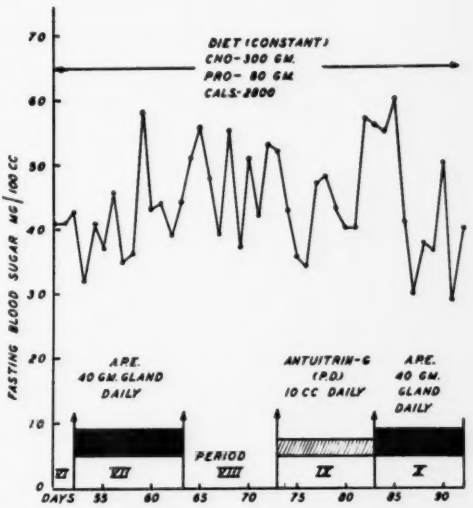


FIG. 3

Periods VII, VIII, IX and X did not give the clear response obtained in the earlier periods. The A.P.E. periods (VII and X) gave average levels of 41 mg. per cent and 42 mg. per cent respectively; rest period (VIII) 48 mg. per cent and antuitrin G period (IX) 44 mg. per cent. While the trend of each response is in the same direction as those obtained in the first five periods, the magnitude of each change is too small to be significant. This lack

[4] To be the subject of a later report.

of responsiveness in the later periods may be due to the gradual development of an anti-insulotropic factor. Such a phenomenon is recognized as occurring under similar circumstances. (See discussion).

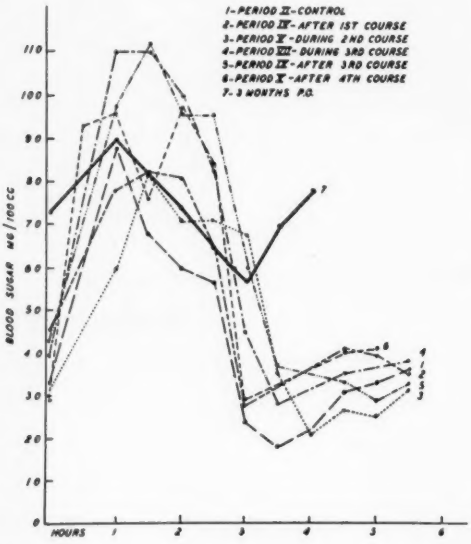


FIG. 4

Dextrose tolerance curves

Serial dextrose tolerance tests (Fig. 4) done before, during and after various courses of A.P.E. injections gave essentially the same response each time (curves 1 through 6). Of special significance is the fact that even after the ingestion of 100 grams of dextrose (given as the test dose each time) the blood sugar never exceeded 110 mg. per cent.

Nitrogen balance

Throughout all periods (except Period I) continuous nitrogen balance studies were made. The subject remained essentially in nitrogen equilibrium during the entire period of study.

Microscopic pathology of surgical specimens

Dr. C. V. Weller reported on the pathology of the specimens as follows:

1. *Liver biopsy*—"Liver tissue is practically normal."

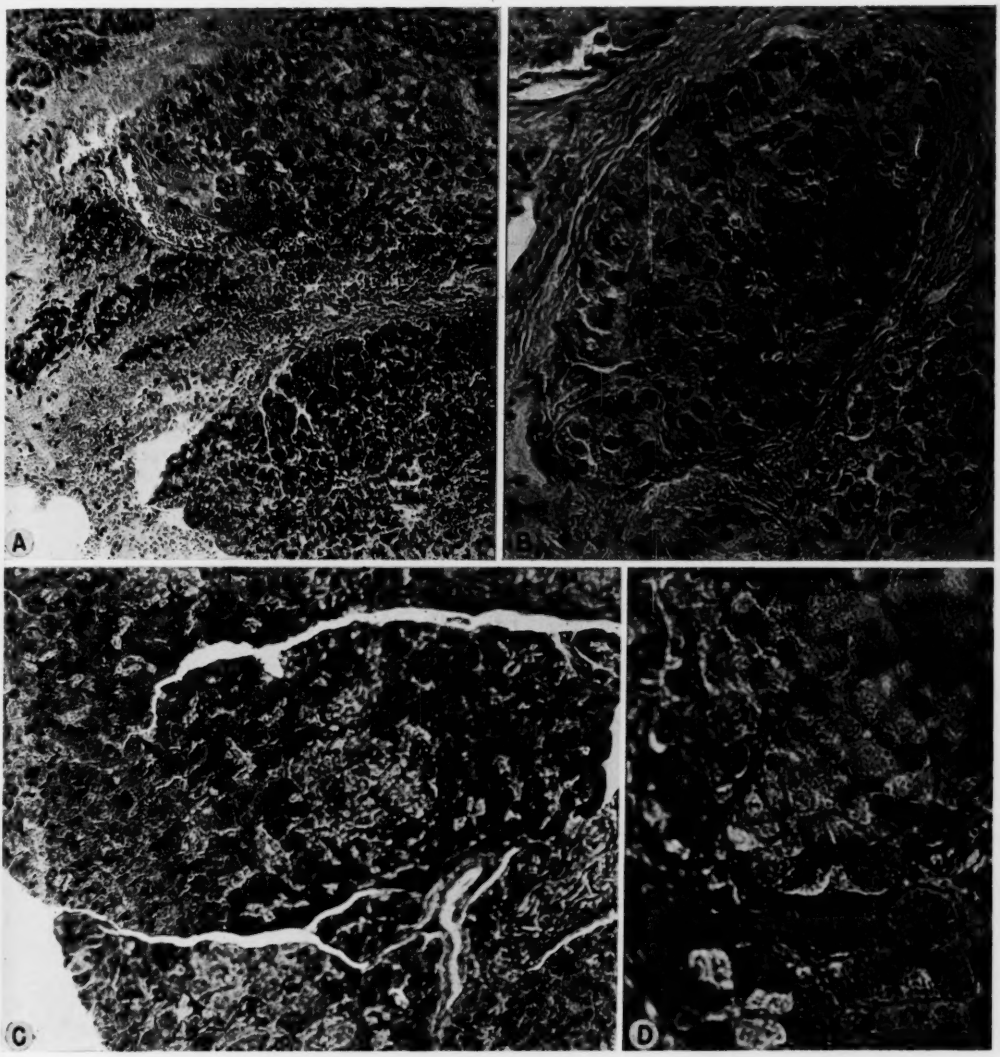
2. *Pancreatic tumor* (Figs. 5 A and B)—'Locally infiltrating adenocarcinoma. The carcinoma grows in the form of cords but is unusually gland-like for an islet cell carcinoma. In the pancreatic tissue about the neoplasm, islets appear in the usual frequency for the body of the pancreas. The islets are small with a reduction in size due to the reduction in size of individual islet cells.

3. *Biopsy of pancreas* (taken from normal portion close to the head of the pancreas, Figs. 5, C and D)—'In sections of a block of this pancreas fixed in Zenkers' fluid and stained with fuchsin—methyl green, there is a sharp differentiation between alveolar epithelium and islet cells. Between the alveoli and sometimes encroaching upon them, there are many small clusters of cells which tinctorially are indistinguishable from the islet cells. They have the same pale staining cytoplasm and while less well supplied with granules, such granules as are present cannot be distinguished from those of the islet cells.

In the islets proper there is no increase in connective tissue. Islets appear somewhat smaller than normal and their cytoplasm is very pale as compared with that of the acinar epithelium. There is a small but prominent nucleolus in a palely stained nucleus. In the cytoplasm minute greenish gray granules and slightly larger fuchsinophilic granules occur in moderate numbers.'

On Figure 6 are shown the results obtained from study of the second patient (*S. B.*, female, aged 41). The sharp fall of the level of the fasting blood sugar during the first course of A.P.E. injections is again demonstrated, the response being identical with that obtained in the first patient. Note, too, the immediate and sharp return of the fasting blood sugar level upon cessation of injections. (At this point the experiment had to be terminated because the patient, having experienced more frequent hypoglycemic attacks during the injection period, felt that the 'treatment' was doing her no good. She refused surgery.)

The two intravenous dextrose tolerance tests on Figure 6 are the pre- and post-'treatment' tests. The latter was done 48 hours after the last injection. It begins with a normal fasting blood sugar level. The response to intravenously administered dex-



FIGURES 5 A-D.

trose, however, is the same as it was before A.P.E. injections were begun. Again there was no evidence of *hyperglycemia* at any time.

DISCUSSION

It is generally agreed that induction of permanent diabetes in dogs by means of injections of A.P.E. is the result of a process which places an insurmountable burden upon the functional activity of the islet tissue, *i.e.*, stimulation to the point of exhaustion and death. But the mechanism by which this intense stimulus is brought about remains unsettled. Because of the fact that there exists in crude A.P.E. a factor which is capable of producing marked hyperglycemia in the hypophysectiomized-depancreatized animal (obviously an extra-pancreatic effect of A.P.E.), it has been assumed that the initial stimulus to the islets of the intact animal is indirect; that the extra-pancreatic effect of

A.P.E. calls forth an increased production of insulin. Two possible ways by which an extrapancreatic influence could conceivably place great pressure upon the functional activity of the islet tissue are either through continuous hyperglycemia or through the action of an insulin antagonist which, by decreasing insulin activity in the tissues, provides a stimulus for increased production of insulin.

The results of our experiments indicate that in two patients harboring an excessive amount of functioning islet tissue, the initial and primary effect of an extract of anterior pituitary gland (shown to be markedly diabetogenic in dogs) is to *intensify* the manifestations of hyperinsulinism. This effect occurs promptly; in the absence of any intervening hyperglycemia; and in the continued presence of excessive insulin activity. We believe that these results afford evidence of the activity of an islet cell-stimulating factor contained in A.P.E.

If one assumes the existence of such a factor, a ready explanation becomes available for many of the apparently contradictory results obtained in animals treated with A.P.E. From this point of view it is of interest to refer briefly to the standard experimental results of A.P.E. injections.

ANATOMICAL AND FUNCTIONAL ALTERATIONS OF THE ISLETS OF LANGERHANS SHOWN TO BE ASSOCIATED WITH INJECTIONS OF A.P.E.

1. Permanent diabetes with histological evidence of degeneration and atrophy of islet tissue (4, 10, 25) can be produced in dogs by injections of crude A.P.E.

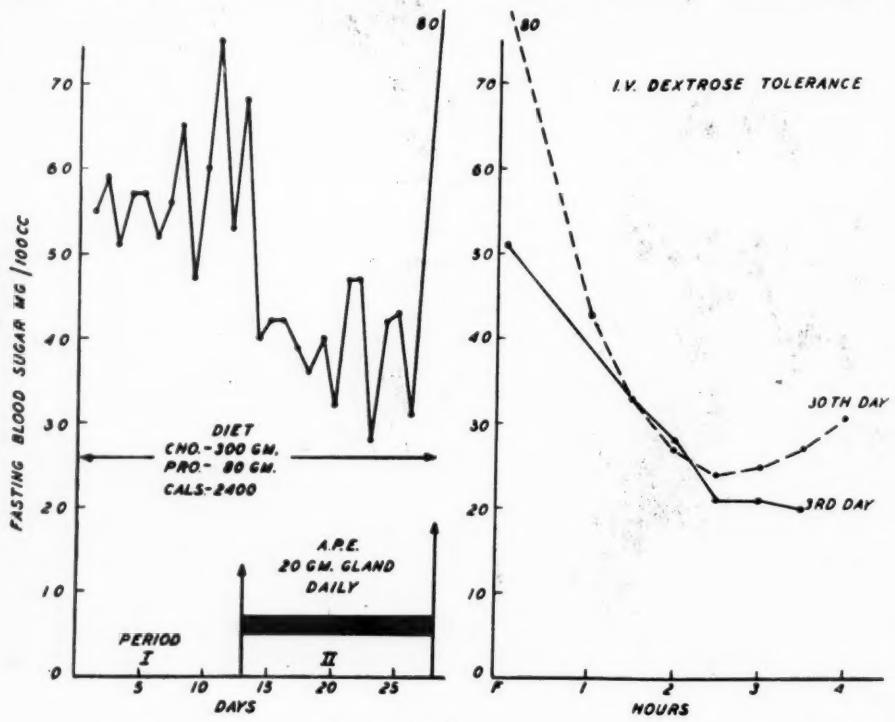


FIG. 6

2. In order to establish permanent diabetes in the dog, large amounts of A.P.E. must be administered over a prolonged period of time (4, 10, 24, 31, 32).

3. During the early period of such administration in the dog, unusual mitotic activity of the islet tissue is demonstrable (25).

4. In the intact dog there always occurs an initial 'resistance period' of several days or

weeks before the blood sugar begins to rise. This is in sharp contrast to the quick rise of blood sugar which occurs in the A.P.E. treated Houssay dog.

5. Some dogs are totally resistant to the hyperglycemic effect of large amounts of A.P.E. Such animals exhibit evidence of normal or increased secretion of insulin following treatment (15, 24).

6. The degenerative effects of A.P.E. upon the islets of the dog can be prevented (and consequently the diabetes, also) by simultaneous administration of insulin. But evidence of increased mitotic activity of the islets is nevertheless observable (2).

7. A normal dog under treatment with A.P.E. may secrete ten to twenty times the normal amount of insulin long before he develops hyperglycemia (33).

8. The same extract which eventually causes diabetes in dogs, doubles the amount of islet tissue in the pancreas of the rat (26). More than twice as much insulin is extractable from the pancreases of the treated rats as from their untreated controls (22). Hyperglycemia does not occur during the development of this result (26).

9. Young A.P.E. treated rats have a consistently lower fasting blood sugar level than their untreated controls and within a few days after treatment exhibit a significant increase in carbohydrate tolerance without any preceding decrease in tolerance (14).

10. No one has yet succeeded in producing diabetes in the intact rat by the use of A.P.E. But the partially depancreatized rat (the pancreatectomy being insufficient in extent to produce diabetes of itself) develops hyperglycemia under such treatment (19).

11. Eighty per cent of rabbits treated with large doses of A.P.E. develop transient glycosuria which quickly disappears despite continued injections. *All* rabbits (whether or not glycosuria occurs) so treated "have twice as much islet tissue by weight" as their controls (23).

12. In A.P.E. treated rabbits there occurs within two hours after the first injection a fall of blood sugar of about 10 mg. per cent, but with repeated injections some go on to develop hyperglycemia (26). In one rabbit of 100 so treated the blood sugar continued to fall to the convulsive level of 20 mg. per cent as a result of four daily injections of the same crude extract which produced diabetes in others (26).

Comment.—We thus have evidence that the same extract which is capable of inducing diabetes under some circumstances produces functional hyperinsulinism and under others, morphological hyperinsulinism; that the *initial* effect of the extract is stimulatory in nature, regardless of whether the final outcome is diabetes or hyperinsulinism; and that hyperglycemia is not the initial stimulus to the islets of Langerhans.

THE ROLE OF HYPERGLYCEMIA IN THE PRODUCTION OF PERMANENT PITUITARY DIABETES

1. A.P.E. administered to the Houssay dog quickly produces a sharp rise of the blood sugar level, this effect obviously being an extra-pancreatic one (16). The factor responsible for this response is relatively heat stable and is incapable per se of producing hyperglycemia in the intact dog. An *additional factor* which is heat labile and which is present in crude A.P.E. prepared and stored in the cold, is required in order to produce diabetes in the normal dog (19).

2. Partially depancreatized cats made diabetic with A.P.E. (the diabetes persisting after withdrawal of treatment) exhibit various degrees of functional and morphological recovery of the islets when the hyperglycemia is reduced (insulin, phloridzin, etc.), provided that such procedures are applied before the hyperglycemia has persisted for more than about three months. Otherwise irreparable damage of the islets ensues (20).

3. Houssay remarks, "The (early) alterations in the islets are due to the anterior pituitary extracts and are not due to the rise in blood sugar, since they do not occur in dogs which have received glucose in a continuous intravenous injection, so as to maintain a blood sugar level as high as that of the anterior-hypophoseal diabetic dogs" (16).

Comment.—While it seems to be true that hyperglycemia, existing by virtue of diminished insular function, is capable of producing

further damage to the islets of Langerhans, evidence is lacking to support the view that the initial effects upon the islets during the induction of diabetes with A.P.E. is the result of an induced hyperglycemia. It would appear, in order for the stimulus of hyperglycemia to injure islet tissue, that such tissue must first be placed in a relatively exhausted state functionally (subtotal pancreatectomy, excessive stimulation with A.P.E., etc.). It is likely that under the circumstances of A.P.E. injections in the dog, a vicious cycle is set up from which the islets cannot escape, *i.e.*, (1) excessive insulotropic stimulation, (2) eventual hypoinsulinism, (3) hyperglycemia, which if sufficiently prolonged leads to (4) complete degeneration of islet tissue.

The difference in the final outcome in the dog on the one hand, and in the rat and rabbit on the other, is dependent upon the ability of the islets to keep pace with the massive stimulus, being quickly overwhelmed in the former and being able to respond in the latter. Experience with the rat (intact versus partially depancreatized) indicates that the total amount of islet tissue available to respond is an important factor in the final outcome. Thus three factors appear to determine the result: (1) the size and frequency of the stimulating dose of A.P.E., (2) the total amount of islet tissue available to respond, and (3) possible species differences in the capacity of the islet cells to respond.

Human beings with organic hyperinsulinism present a very special situation and a unique opportunity to observe the immediate rather than the secondary effects of the stimulating factor. We know in these cases, before any A.P.E. is administered, that there exists a great excess of functioning islet tissue. The blood sugar is persistently low and and convulsive attacks are frequent. The reserve of islet tissue is so large that it is capable of responding at once and fully to an insulogenic stimulus. The results of our experiments are in line with this interpretation.

Theoretically, if the stimulus could be made sufficiently large in relation to the capacity of the islet tissue to respond (such as the relation between the stimulus and the reserve supply in the dog) we should expect eventual degeneration of all islet tissue, tumor tissue included.

DIABETES MELLITUS VS. ORGANIC HYPERINSULINISM

It is conceivable that clinical diabetes mellitus and organic hyperinsulinism have a common basis of origin; that organic hyperinsulinism represents the exceptional response within the species to the same stimulus to the islets which usually results in the development of diabetes.

Clinically, there is much to suggest that impairment of anterior pituitary function (X-ray irradiation, destructive processes, surgery, etc.) occurring in the course of well established diabetes results in amelioration of the disease. But *the mode of induction of the usual type of clinical diabetes remains unanswered*, involving among other variables an hereditary aspect.

In *unusual* types of clinical diabetes, on the other hand, there is a good deal of evidence to support the idea that excessive activity of the anterior hypophysis is responsible for the production of the disease. It is frequently pointed out that the high incidence of diabetes in cases of pituitary basophilism (Cushing's Disease) and pituitary eosinophilism (acromegaly, etc.) represents the clinical counterpart of the experimental induction of diabetes in normal animals by means of injections of A.P.E.

It is of considerable interest, therefore, to note that a significant number of proved cases of organic hyperinsulinism (in which complete autopsy material is available) have shown abnormalities of the pituitary gland similar to those found in association with diabetes mellitus (12, 21, 27, 28). Further clinical and pathological investigation of this relationship seems indicated. In this connection, the occasional finding of generalized hyperplasia of the islets of Langerhans *in association with* multiple islet cell adenomata (8, 18) suggests the activity of an islet cell stimulating substance. Frazer (11) and others arrive at the interesting conclusion that "a patient with acromegaly may be at the stage of 'com-

pensatory hyperinsulinism' or may end by having hypo-insulinism like a 'Young dog'."

The term "dysinsulinism" has been suggested (13) to denote a condition in which the patient presents evidence of diabetes at one time and of hyperinsulinism at another, and in some cases, evidence of both at the same time. This situation is not a proved clinical entity. But the occasional case (17) of unquestioned diabetes which gradually becomes milder and finally ends as one of severe paroxysmal spontaneous hypoglycemia demands our attention. A similar case (3) was shown at autopsy to have develped an islet cell carcinoma. Harris (13) mentions three diabetic patients whose hyperglycemia was preceded by a period of hyperinsulinism. He also states that 'the familial tendency exists in hyperinsulinism as in diabetes.' Others have commented upon the unusually high incidence of diabetes in the family background of patients with hyperinsulinism.

SUMMARY

Two patients suffering from organic hyperinsulinism were given daily injections of anterior pituitary extract and the response obtained was compared with that observed in dogs receiving the same extract. The results indicate that the extract employed is 'diabetogenic' when administered to dogs; that the induction of hyperglycemia in dogs by daily injections is associated with a latent period varying from several days to several weeks (a consistent finding observed by all investigators); that the same extract which is *eventually* hyperglycemia-producing in dogs is *promptly* hypoglycemia-producing in humans harboring an excessive amount of functioning islet tissue; and that cessation of injections allows the blood sugar to return quickly to or above its original level. During the course of treatment with A.P.E., dogs show a gradual decrease in tolerance for carbohydrate while no decrease from the initially excessive tolerance is observable in these patients.

It is reasonable to conclude from these findings that the initial and primary response of islet tissue to the so-called "diabetogenic principle" is one of prompt stimulation. In order that this response be brought out clearly it is necessary to have an abnormally large amount of functioning islet tissue available to respond, so that the secondary effect (islet fatigue) of an overwhelming stimulus does not soon overshadow the primary activity of the substance (as it does in the dog). This requirement is provided in patients having secreting pancreatic insulomata.

In the later periods of injection of A.P.E. in one patient neither a hypoglycemic nor a hyperglycemic effect was obtained. The fact that the fasting blood sugar level remained low indicates that excessive amounts of insulin continued to be secreted. But no *further* lowering of the blood sugar was obtainable, as it had been during the initial injection periods. During this same period no decrease in tolerance for carbohydrate was demonstrable to indicate that the lack of hypoglycemic response was due to islet fatigue. The only ready explanation for this finding is the possibility that an anti-insulotropic substance had been built up during the first three to four weeks of injections. This type of response to continued administration of pituitary extracts is known to occur (5, 28).

CONCLUSIONS

1. Crude A.P.E. prepared and stored in the cold contains an insulogenic or insulotropic principle which acts by stimulating directly the insulin producing cells of the islands of Langerhans.

2. The exhausting effect of this principle upon the islets of Langerhans is responsible for the initiation of hyperglycemia in normal dogs. This substance is not the same as that which produces hyperglycemia in the Houssay animal.

3. The sequence of events during the induction of *permanent* diabetes in the normal dog by means of A.P.E. is (1) a direct and excessive stimulation of the islands of Langerhans; (2) a gradually diminishing ability of the islets to respond to the persistent stimulus with consequent decrease of insulin production; and (3) hyperglycemia, which, if sufficiently prolonged, carries the process of islet

cell degeneration to completion. Hyperglycemia, *per se*, constitutes a burden upon the *already debilitated islets* and may set up a vicious cycle from which the islets cannot escape.

4. When the islets are able to respond to the insulogenic stimulus with sufficient intensity to avoid being overwhelmed by it, the result obtained is not diabetes but hyperinsulinism (morphologically and functionally). This response occurs in the absence of hyperglycemia and cannot, therefore, be attributed to a stimulus stemming from an elevated blood sugar level.

5. Factors which determine whether the stimulus will result in diabetes or in hyperinsulinism are: 1, duration and intensity of the stimulus, 2, total amount of functioning islet tissue available to respond, and 3, species differences in islet tissue reactivity.

6. When conditions are such that there exists an abnormally great abundance of functioning islet tissue (as is the case in human organic hyperinsulinism) the principle response to the so-called "diabetogenic" factor becomes clearly evident. It consists of a prompt, sharp, further fall of the blood sugar level without any intervening hyperglycemia, and a rapid return when injections are stopped. This is in sharp contrast to the prolonged lag period which is necessary for the induction of hyperglycemia in normal dogs. The hyperglycemia thus produced is a phenomenon secondary to intense activity of the insulotropic substance upon the islet cells with eventual fatigue.

7. It is considered likely that clinical diabetes mellitus and, at least, some cases of organic hyperinsulinism have a common basis of origin, the latter representing the exceptional response within the species to the same insult which usually produces the former.

CASE REPORTS

Case #1. A. P., aged 25, white, single laborer. Admitted 10-28-42.

C.C.—'Spells.'

P.I. The patient had been perfectly well until his initial attack in August, 1941. While at work at 11:30 a.m. he suddenly became very weak and lost consciousness. He awoke spontaneously in 30 minutes and had his lunch. There was no further trouble until a similar episode at 4:30 p.m. occurred in December, 1941.

In mid-January, 1942, attacks became more frequent and progressed in frequency and severity up until the time of admission to the University Hospital. They began to occur most frequently in the early morning hours (4:00 a.m. to 7:00 a.m.) but often occurred three to four hours following the preceding meal. Premonitory symptoms were hunger, tension, weakness, sweating and visual disturbances. This was followed by a semi-lucid period during which he was aware that he could not control his muscular movements. He knew that he was unable to comprehend commands during this period although he heard them. Complete loss of consciousness was often associated with generalized convulsive movements.

He did not believe that convulsions occurred during those attacks in which he was found to be unconscious in bed before breakfast. The patient's sister, with whom he was living, has a diabetic child receiving daily injections of insulin. The sister having noted the similarity of his symptoms to those of her child during insulin reaction, found that he, too, could be quickly revived by the administration of orange juice. The patient then learned that he could ward off day-time attacks by the ingestion of food if he acted promptly.

By the time of admission attacks had progressed in frequency to an average of two per week. The patient's weight had been constantly at about 150 pounds for several years.

P.E. The patient was a very well developed, healthy looking, young male. B.P. 100/60. No physical defects could be elicited on examination.

Laboratory Data. Blood counts, urine examination and Kahn tests were negative. Spinal fluid, negative. B.M.R.: −4 per cent. Serum proteins: total 7.8 gm. per cent, albumin 4.6 gm. per cent, globulin 3.2 gm. per cent. Bromsulphalein (5 mg./Kilo—30 minutes): less than 15 per cent retention. Cholecystogram showed a normally functioning gall bladder without evidence of stone. X-ray of the skull was negative. Glucose tolerance test after standard dietary preparation (8) (9) was:

F.	31 mg. per cent
1 h.	101
2 h.	83
2½ h.	77
3 h.	52
3½ h.	37
4 h.	31
4½ h.	25
5 h.	44
5½ h.	31
6 h.	29

Daily fasting blood sugar values ranged from 12 to 60 mg. per cent; the majority from 25 to 35 mg. per cent. Blood sugar values during spontaneous attacks ranged from 9 to 30 mg. per cent.

After the investigative program (see text) had

been completed the patient was operated upon by Dr. F. A. Coller. A firm, round, well encapsulated mass, 1 cm. in diameter was found to be deeply embedded in the body of the pancreas. This with a surrounding portion of pancreatic tissue was removed (Figs. 5 A and B). A biopsy of the normal portion of the pancreas (Figs. 5 C and D) and of the liver was also obtained. (For microscopic findings see under 'Results')

The morning after operation the fasting blood sugar was 115 mg. per cent. For the next seven days it was 73, 63, 98, 78, 83, 92, and 82 mg. per cent respectively. A glucose tolerance test (after standard dietary preparation) 3 months post-operatively was:

F.	72 mg. per cent
1 h.	90
2 h.	73
2½ h.	64
3 h.	52
3½ h.	66
4 h.	74

The patient has returned to his job and has remained perfectly well for the past two years.

Case #2. B. S., aged 41, white, married housewife.

C.C. Increasing fatigue, dizziness, and spells of unconsciousness.

P.I. This patient has been followed during multiple admissions and several out-patient visits to the University Hospital since June 6, 1939. The essentials of her history are recorded below.

There had been intermittent difficulty in eating solid foods since January, 1939. For the most part she had subsisted on a liquid diet. There had been frequent periods of fatigue and dizziness. On May 22, 1939, she had lapsed into an unconscious state in which she remained for four or five hours until 'I.V. fluids' were given at a local hospital. Admitted on the Otolaryngology Service on June 6, 1939, for correction of esophageal obstruction, she was found to have severe cardiospasm. Esophageal dilation allowed normal food intake and she became entirely asymptomatic.

She remained well until April, 1941, when fatigue dizziness, irritability and drowsiness began to appear in attacks. On May 16, 1941, several teeth were extracted by her local dentist. That evening she became semi-stuporous but recovered in two hours. Two days later a similar attack led her local physician to give her a total of 70 units of insulin (50 u. and 20 u.). She was sent to University Hospital in a semi-comatose state. She had gained from 140 to 186 lbs. in the interval. Consciousness was quickly restored by means of intravenous glucose. For the next two days the fasting blood sugar was 28 mg. per cent and 23 mg. per cent respectively. During a spontaneous attack at 1:00 p.m. no the third day the blood sugar was 22 mg. per cent. Oral glucose tolerance test after seven days of standard dietary preparation (8, 9) was as follows:

F.	49 mg. per cent
½ h.	66
1½ h.	107
2 h.	108
2½ h.	104
3 h.	87
3½ h.	48
4 h.	38

During this admission cardiospasm again became a serious problem but was well controlled by the use of nitroglycerine sublingually before meals. It was noted that the cardiospasm was intimately related to the hypoglycemia, never occurring unless the blood sugar first became low. She was advised to remain for the various tests designed to exclude other possible causes of spontaneous hypoglycemia. She was told that she probably had a pancreatic adenoma which would require surgery. She asked to be discharged.

Her final admission to the University Hospital was eighteen months later (11-18-42). In the interim she had been eating well, having gained 17 pounds more (wt. now 203 lbs.). She had been continuously aware of mid-morning and mid-afternoon weakness, but had had no other symptoms until one month before. At that time attacks of unconsciousness, lasting from 15 minutes to several hours, began to occur again, usually coming on in the early afternoon or evening. Such an attack would always occur, if for any reason she missed a meal. For the past two weeks attacks had been occurring daily. The day before admission she had been unconscious from 1:00 p.m. to 6:00 p.m. The attack had been terminated by the administration of glucose intravenously.

P.E. The patient was a very obese woman (5′ 4″—203 lbs.) who did not appear ill, but who exhibited marked emotional lability. The B.P. was 138/92. The only abnormal physical findings besides the obesity were, 1. an adenomatous thyroid, and 2. hyperactive reflexes.

Laboratory data. Blood, urine and Kahn reaction were negative. Blood bilirubin 0.3 mg. per cent. Hippuric acid test (I.V.—1 hour) 1.16 and 1.28 gms. Bromsulphalein (5 mg./Kilo—30 minutes) 10 per cent retention, N P N—20 and 30 mg. per cent. Serum proteins—total 6.6 gm. per cent, albumin 3.1 gm. per cent, globulin 3.5 gm. per cent. Cholecystogram showed non-visualization of the gall bladder without evidence of stone. B.M.R. plus 3 per cent.

At this point our studies were begun (See Text). At the conclusion of the studies operation was refused and the patient was discharged against advice.

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Observations on 78 Thyrotoxic Patients Treated with Thiouracil

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Inasmuch as nearly 12 per cent of all cases treated with thiouracil have shown reactions of lesser or greater degree (38) it seems essential to collect data from large groups of patients before giving unqualified support to its widespread use. We reviewed the entire literature to June 1, 1944 (38). Since that time at least 58 articles on thiouracil have appeared (3–38, 40–42, 44–52, 54–64), of which 34 (3–7, 9–11, 14–16, 19, 22, 23, 25–27, 29, 30, 34–38, 40–44, 46, 50–52, 57, 59–62) summarize data from not less than 500 patients.

I. MATERIAL AND METHODS

Ten male and 68 female patients with thyrotoxicosis were studied while under treatment with thiouracil[2] (Table 1) for periods ranging from two weeks to 16 months (Table 2).

Forty-one patients were allowed to continue their usual routine of living. The remainder were hospitalized for long or short periods to permit continuous observation and more thorough investigation. Except for their confinement in the hospital these patients

Table 1. Age and Sex Distribution in 78 Cases of Thyrotoxicosis Treated with Thiouracil

Type of goitre	Total No.	Male			Female		
		No.	Age (yrs.)		No.	Age (yrs.)	
			Range	Av.		Range	Av.
Hyperplastic	53	6	25–64	46.5	47	14–65	40.1
Nodular	25	4	46–65	50.7	21	31–67	47.7
	78	10			68		

Table 2. Treatment of 78 Thyrotoxic Patients with Thiouracil

Months of treatment	No. cases under treatment	Treatment		Remarks
		Discontinued in	Resumed in	
0	78			
½	76	2	0	1 operated 1 toxic
1	68	8	3	5 operated
2	59	7	1	1 operated
3	52	3	3	
4	45	1	0	
5	42	2	1	
6	37	2	0	
7	28	3	0	1 operated
8	19	4	1	
9	18	1	1	
10	14	1	1	
11	9	0	0	
12	7	0	0	
13	4	0	0	
15	3	0	0	
16	0	0	0	

[1] Emmanuel Maynz Fellow in Research.

[2] Thiouracil used in the pursuit of these studies was furnished through the courtesy of Drs. B. W. Carey and Stanton M. Hardy of the Lederle Laboratories, Pearl River, N. J.; their kindness is gratefully acknowledged.

were encouraged to conduct themselves as they would at home; no special diets, periods of rest, or drugs (with the exception of thiouracil) were used.

Various routines for the administration of thiouracil have been used in the course of these studies, but that which is now commonly employed follows:

TABLE 3. DAILY DISTRIBUTION OF THIOURACIL MEDICATION

Total dose daily	2 tablets given at	1 tablet given at
gm. tab.		
0.8 8	7 a.m. and 10 p.m.	10 a.m. and 1, 4, and 7 p.m.
0.6 6	0	7 and 10 a.m., and 1, 4, 7 and 10 p.m.
0.4 4	0	7 a.m., 12 noon, and 5 and 10 p.m.
0.3 3	0	7 a.m., 2 and 10 p.m.
0.2 2	0	8 a.m. and 8 p.m.

Other features of the regimen, including a description of laboratory methods, have been previously described (38, 53).

II. RESULTS

A. Change in subjective symptoms and physical findings

The more commonly mentioned symptoms and observed signs are included in Table 4. A "sense of well being" was usually experienced by the patient long before specific subjective complaints or objective phenomena showed any appreciable change. This ill-defined feeling of improvement has been known to make its appearance as early as the third day, and was usually present by the end of the first week. The term "nervousness" was used quite loosely by most patients and in some instances could not be further clarified or amplified.

The *pulse rate* was almost invariably lower after treatment, although in 4 instances it did not return to normal, even after several months of care. One of these four patients was in severe cardiac failure when treatment was begun. The other three showed no clinical or electrocardiographic evidences of myocardial damage, although some may have been present. Of the 30 patients with a pretreatment systolic blood pressure exceeding 150 mm. of mercury, three had a known history of essential hypertension. The remaining 5, in whom the pressure did not fall below 150 mm. of mercury under treatment, were believed to be suffering from a benign form of hypertension, as the diastolic pressure in each instance was 90 mm. of mercury or below. *Exophthalmos* was present in 38 of 78 patients (Tables 4 and 5). In no instance, was an increase in the exophthalmos observed under treatment. This may simply mean that we had no instances of the thyrotrophic form of exophthalmos in the entire series of cases (43).

TABLE 4. CLINICAL FINDINGS IN 78 THYROTOXIC PATIENTS TREATED WITH THIOURACIL

Symptoms and signs	Number of Patients			
	Initially present	Not mentioned	First symptom to disappear[1]	Absent after treatment
"Nervousness"	78	0	35	78
Apprehension	62	16	29	62
Palpitation	44	13	14	41
Insomnia	38	24	17	38
Voracious appetite	45	22	3	41
Anorexia	11	22	0	11
Weakness	19	49	0	19
Diarrhea	7	0	0	7
Sweating	65	8	0	65
Pulse above 100	52	0	0	48
Systolic B.P. above 150 mm. Hg.	30	0	8	22
Pulse pressure greater than diastolic pressure	26	0	0	19
Loss of weight	78	0	18	78
Enlarged thyroid	65	0	0	20[2]
Exophthalmos	37	0	0	17[3]
Fibrillation	18	0	0	15

[1] In some instances two of these were believed to disappear simultaneously or nearly so.
[2] Decreased only—see tab. #6.
[3] Decreased only—see tab. #5.

An initially *large thyroid* gland was encountered in 65 patients, of whom 41 had a hyperplastic, and 24 a nodular goiter (Table 6).

The *fibrillation* present in 18 cases prior to treatment was believed to reflect, at least in part, the abnormal cardiac load arising from the thyrotoxicosis. Digitalis was purposely

TABLE 5. EXOPHTHALMOS IN 78 THYROTOXIC PATIENTS TREATED WITH THIOURACIL

	Hyperplasia				"Adenoma"			
	Total No. cases	De-creased	Un-changed	In-creased	Total No. cases	De-creased	Un-changed	In-creased
Before Treatment	29	—	—	—	9	—	—	—
Under Treatment	26	13	13	0	9	4	5	0
B.M.R. still high when observation made	—	4	1	0	—	0	1	0
Effect of Treatment not mentioned	3				0			

not given to any of these patients until the thyroid condition was brought under control, and then only if the fibrillation had failed to disappear under thiouracil therapy alone. In six of the ten patients with hyperplasia, a normal rhythm was resumed under thiouracil therapy alone. In one of these, a Wilson type of bundle branch block was present which was not influenced by the thiouracil. Two of these ten patients developed a normal rhythm when digitalis was added, and in two the fibrillation remained unchanged despite both thiouracil and digitalis. In the nodular group six of eight patients developed a normal rhythm under treatment with thiouracil alone; one more reverted to a normal sinus mechanism when digitalis was also administered, and one remained resistant to both types of therapy. Under previous therapy with digitalis and iodine in four of the hyperplastic variety and in two of the nodular type of goiter, no change in the associated fibrillation had been obtained.

Previous operation had been performed in 10 of the 53 patients with a hyperplastic goiter and in 8 of the 25 with a nodular gland. Multiple operations had been done in three patients. These surgical procedures appeared to exert no influence upon the action of thiouracil in relieving all toxic manifestations of either type of goiter.

B. Laboratory data

The correlation of objective clinical and laboratory data are well illustrated in Figure 1, (*case No. 64*). This figure graphically describes the case of a 44 year old woman, whose symptoms had started two years prior to the beginning of therapy. Since that time she had complained of palpitation, cold clammy perspiration particularly of the hands and feet, and nervousness. She was 60.25 inches tall and despite a 10 pound loss of weight in one year was still much overweight at 154 pounds. Eye signs of thyrotoxicosis were absent. The confirmatory findings included a diffuse soft enlargement of the thyroid, a fine tremor of the tongue and hands, tachycardia (initial

TABLE 6. CHANGES IN THE SIZE OF THE THYROID WHILE UNDER TREATMENT WITH THIOURACIL

Status of gland	Hyperplasia			"Adenoma"		
	No. cases	Average		No. cases	Average	
		Mos. of Rx.	B.M.R. when change noticed		Mos. of Rx.	B.M.R. when change noticed
Initially						
Large	41	—	—	24	—	—
Normal	9	—	—	0	—	—
Scarred	3	—	—	1	—	—
After Treatment						
Further enlargement	11	2.8	+4.6	10	5.3	+ 3.1
Decrease in size	14	0.9	+9.1	6	0.7	+22
Decrease and then increase	2			2		
Not mentioned	6			2		

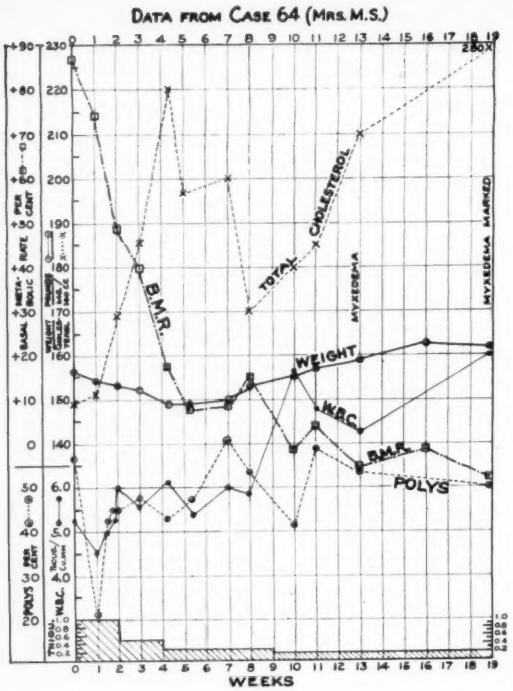
DATA FROM CASE 64 (MRS. M.S.)
B.M.R.
TOTAL CHOLESTEROL
WEIGHT
W.B.C.
R.M.R.
POLYS
MYXEDEMA
MYXEDEMA MARKED
WEEKS

FIG. 1

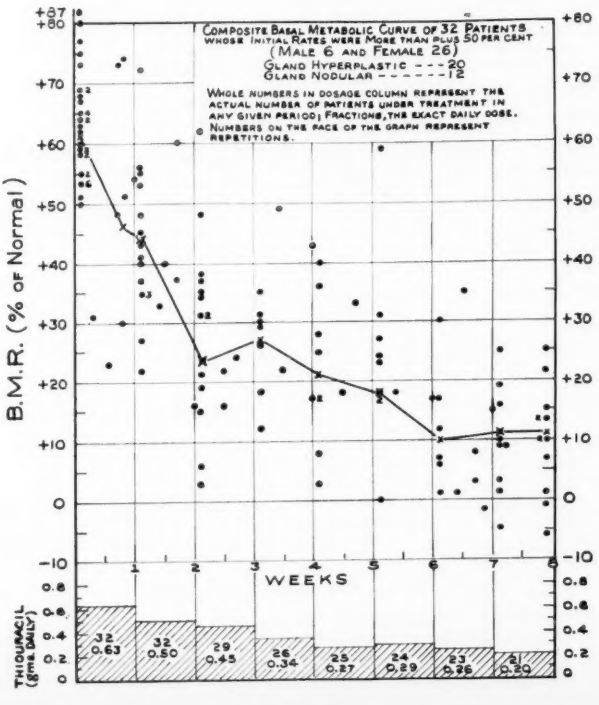
COMPOSITE BASAL METABOLIC CURVE OF 32 PATIENTS WHOSE INITIAL RATES WERE MORE THAN PLUS 50 PER CENT
(MALE 6 AND FEMALE 26)
GLAND HYPERPLASTIC - - - 20
GLAND NODULAR - - - - - 12
WHOLE NUMBERS IN DOSAGE COLUMN REPRESENT THE ACTUAL NUMBER OF PATIENTS UNDER TREATMENT IN ANY GIVEN PERIOD; FRACTIONS, THE EXACT DAILY DOSE. NUMBERS ON THE FACE OF THE GRAPH REPRESENT REPETITIONS.
B.M.R. (% OF NORMAL)
WEEKS
THIOURACIL (GMS. DAILY)
32 0.63
32 0.50
29 0.45
26 0.34
25 0.27
24 0.29
23 0.26
21 0.20

FIG. 2

rate 140 per minute), hypermotility of the heart, and hyper-active reflexes. The patient was believed to have a forme fruste type of toxic hyperplasia. Under treatment it will be noted from Figure 1 that the basal metabolic rate and the blood cholesterol moved inversely to each other, and that the cholesterol exceeded high normal levels while the metabolic rate was still plus 18. A later adjustment took place in this figure only to give way to abnormally high values as a myxedematous state was reached. Moreover, it seems important to emphasize the fact that myxedema occurred when the basal metabolic rate was minus 8. The weight changes in this case are rather typical with an initial decrease and subsequent increase, although in underweight individuals the increment often begins somewhat earlier, *i.e.* in the second week. The decrease in weight during the myxedematous phase was seen in all of the four patients who developed the condition and is thought to be due to the heightened irritability, nervousness and insomnia which occurs.

The marked decrease in the leucocyte and polymorphonuclear cell counts occurred at the end of the first week, in *Case number 64*, that is somewhat earlier than usual (Fig. 1). Treatment was not stopped because of the rapid return to normal within 24 hours, and the complete absence of subjective symptoms commonly seen in the toxic or hypersensitivity individual. Notice the slight increase in the total number of white blood cells appearing in the tenth week of treatment. This is a common phenomenon frequently occurring immediately after a depression at any time during treatment and commonly much more pronounced than seen here.

1. *The basal metabolic rate*

Composite curves of serially taken basal metabolic rates in the hyperplastic and nodular groups revealed no difference in the speed with which the two groups reacted to thiouracil. However, when we compared the group of individuals which had basal metabolic rates above 50 with those below that figure, it was obvious that the drop in the former on a percentage basis was much greater during the first two weeks than was that of the latter (Fig. 2 and Fig. 3).

2. *Blood cholesterol*

Initial values for blood cholesterol were high, *i.e.*, above 200 mg. per 100 cc., in 11 of 52 patients upon whom performed. All of these had satisfactory evidence of thyrotoxicosis, but in two the high cholesterol could have been attributed to an uncontrolled diabetes. In 36 patients, serial examinations were made while patients were under treatment. In 31, these studies were done at approximately two week intervals until the thyrotoxicosis was controlled and less frequently thereafter.

The relation between the concentration of cholesterol in blood and the degree of elevation of the basal metabolic rate was of interest. In 12 of 31 patients the cholesterol exceeded 200 mg. per 100 cc. when the basal metabolic rate was between plus 10 and plus 15 per cent, and in an additional 14 exceeded that value when the basal metabolic rate varied between plus 5 and plus 10 per cent. In other words, approximately 84 per cent of the patients showed somewhat elevated cholesterol values when the basal metabolic rate was between plus 5 and plus 15 per cent. The general clinical condition of the patient was always satisfactory with basal metabolic rates within such a range, and usually at its best when the metabolic rate was between plus 10 and plus 15.

Despite these facts, the absolute level of the blood cholesterol was hardly of as great importance as the percentage changes from the initial levels in each individual patient. This is readily shown in Fig. 4, which is a composite curve of the percentage changes in blood cholesterol plotted against the basal metabolic rates. In this curve the initial value for blood cholesterol in each individual patient is taken as 100 per cent, and subsequent values are figured as a percentage deviation therefrom. While there was a great deal of "scattering" of the figures here plotted, the mean values and standard deviation permit the conclusion that a straight line relationship apparently exists between the

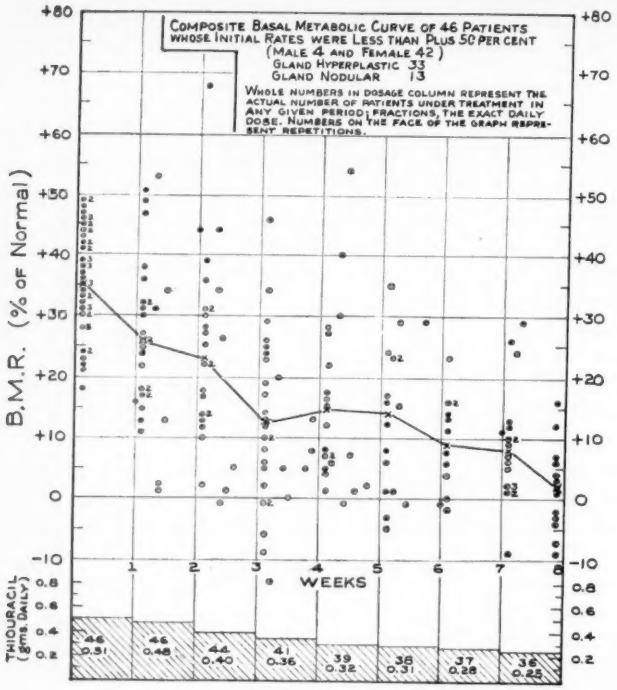
COMPOSITE BASAL METABOLIC CURVE OF 46 PATIENTS WHOSE INITIAL RATES WERE LESS THAN PLUS 50 PER CENT
(MALE 4 AND FEMALE 42)
GLAND HYPERPLASTIC 33
GLAND NODULAR 13
WHOLE NUMBERS IN DOSAGE COLUMN REPRESENT THE ACTUAL NUMBER OF PATIENTS UNDER TREATMENT IN ANY GIVEN PERIOD; FRACTIONS, THE EXACT DAILY DOSE. NUMBERS ON THE FACE OF THE GRAPH REPRESENT REPETITIONS.
B.M.R. (% OF Normal)
+80
+70
+60
+50
+40
+30
+20
+10
0
-10
WEEKS
1
2
3
4
5
6
7
8
THIOURACIL (gms. DAILY)
0.8
0.6
0.4
0.2
46 0.51
46 0.48
44 0.40
41 0.36
39 0.32
36 0.31
37 0.28
36 0.25

FIG. 3

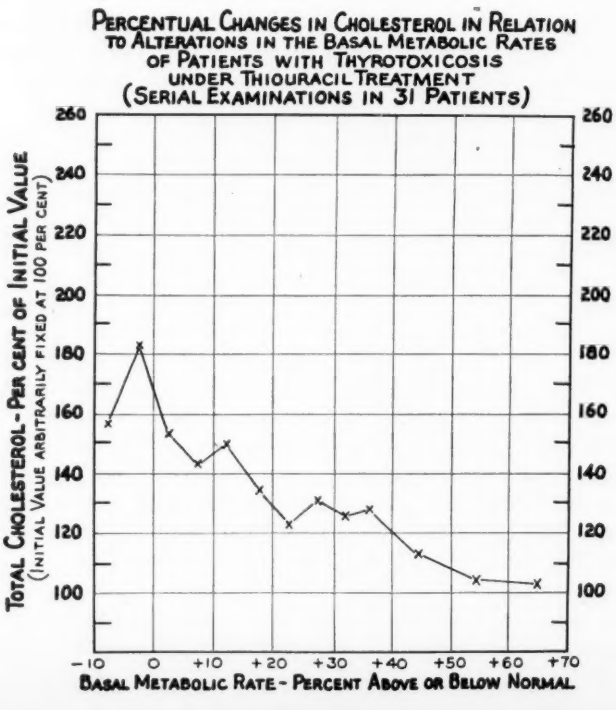
PERCENTUAL CHANGES IN CHOLESTEROL IN RELATION TO ALTERATIONS IN THE BASAL METABOLIC RATES OF PATIENTS WITH THYROTOXICOSIS UNDER THIOURACIL TREATMENT
(SERIAL EXAMINATIONS IN 31 PATIENTS)
TOTAL CHOLESTEROL - PER CENT OF INITIAL VALUE
(INITIAL VALUE ARBITRARILY FIXED AT 100 PER CENT)
260
240
220
200
180
160
140
120
100
-10
0
+10
+20
+30
+40
+50
+60
+70
BASAL METABOLIC RATE - PERCENT ABOVE OR BELOW NORMAL

FIG. 4

percentage increase in the blood cholesterol and the decrease in the basal metabolic rate.

3. *The blood picture*

In two patients, anemia in which the erythrocyte count was 3.5 million or less and the hemoglobin 65 per cent or less has been encountered after several months of treatment. One of these patients was relieved by the administration of iron by mouth while thiouracil was continued; in the other, thiouracil was stopped and an operation performed.

The behaviour of the leucocytes of patients under treatment with thiouracil is summarized in Table 7. Leukopenia, that is, 5,000 or less leucocytes per cu mm. was encountered in the pretreatment period in 5 of 78 cases; none of these had a relative granulocytopenia; that is, less than 50 per cent polymorphonuclear leucocytes in the stained smear. However, there were six instances of relative granulocytopenia in which the total leucocyte count was normal. All of these abnormalities disappeared under treatment with thiouracil without any exacerbation of the initial or pretreatment disturbance.

On the other hand, 11 patients developed a leukopenia, and 14 a relative granulocytopenia, while undergoing treatment with thiouracil (Table 7). The majority of these reactions appeared between the second and third weeks of treatment with an over-all average for the former of 2.8 weeks and for the latter of 3.5 weeks. All of them disappeared without interfering in any way with the therapeutic regimen. Severe leukopenia with agranulocytosis occurred in two patients (*Cases 22* and *34*), and necessitated discontinuance of the drug. Both patients were seriously ill, but recovered completely in from 10 to 13 days, one following a series of transfusions and injections of pentnucleotide, and the other following a policy of watchful waiting during which fluids were forced to favor excretion of the drug. These are reported in detail elsewhere (39). The first of these had received approximately 21 gms. of drug at the rate of 0.5 gm. daily. She developed a sore throat and bleeding of the gums two days prior to the complete disappearance of the granulocytes.

The second patient had been on graded doses of the drug for two months, beginning with 0.6 gm. daily, and was receiving 0.2 gram daily at the time of the reaction. On the tenth day of treatment and on several subsequent occasions prior to the development of the agranulocytosis either leukopenia or abnormal white forms in the stained smears had been observed. In this patient the onset of fever and disappearance of granulocytes were simultaneous.

TABLE 7. DATA FROM BLOOD COUNTS IN 78 PATIENTS WITH THYROTOXICOSIS UNDER TREATMENT WITH THIOURACIL

	Leukopenia (<5,000 cells cu. mm.)			Relative granulocytopenia (Polys<50%)		
	No. cases	Week of appearance		No. cases	Week of appearance	
		Range	Average		Range	Average
Pretreatment	5	—	—	6	—	—
Appearing and Disappearing during Treatment	11	1 to 6	2.8	14	1 to 16	3.5
Reaction Necessitated stopping Drug	2	1.5 to 6	3.8	2	1.5 to 6	3.8

C. Toxic reactions

1. *Those which disappeared without altering the course of therapy.*

Generalized pruritus occurred in five patients; rashes, most marked over the forearms and legs in three; edema, most marked about the eyes and around the ankles in three; diarrhea in one; and dryness of the mouth with excessive thirst, in one. Reference has already been made to leukopenia and granulocytopenia.

2. *Those which necessitated cessation of therapy*

Two patients with agranulocytosis have already been discussed. In two additional patients, the onset of a chill associated with high temperature, urticarial rashes, sore-throat and symptoms of "the grippe" necessitated the discontinuance of therapy. Each of these patients, whose reactions are detailed elsewhere (39), recovered completely in about ten days. In each, a subsequent single dose of the drug reproduced within six hours the entire syndrome in a somewhat milder form. The hypersensitive rather than the toxic nature of this type of reaction seems to be confirmed.

Myxedema has been observed in four patients, two of whom had hyperplastic and two had nodular goiters. Their lowest basal metabolic rates were minus 8, minus 12, minus 11, and minus 15 respectively. In one, the myxedematous state was complicated by cardiac failure, so that it is quite possible that her lowest recorded basal metabolic rate of minus 8 was considerably higher than was to be expected as a result of the thyroid status alone. All of these patients recovered spontaneously after cessation of the drug; restitution began at approximately five days and was completed within two weeks. It is easy to avoid myxedema by keeping the basal metabolic rate above plus 5. The state was purposely induced in three of the four patients above in order to study serial changes in capillary permeability. The fourth patient had failed to keep several appointments but had continued "the greater than maintenance dose" of the drug previously prescribed. In all of these four patients the drug was resumed at "maintenance" levels when the basal metabolic rates had returned to between plus 10 and plus 15 per cent.

D. The influence of thiouracil on diabetes mellitus in the thyrotoxic patient

Eleven of our 78 thyrotoxic patients had a pre-existing diabetes mellitus; five of these were associated with a hyperplastic goiter and six with a nodular type. During the period of treatment with thiouracil the tolerance of one of these patients decreased as shown by the need for a permanent increase in the dosage of protamine zinc insulin from 40 to 50 units daily. However, this change in tolerance occurred subsequent to an intercurrent pneumonic infection and was probably due to it. In three patients, there was no change in tolerance. All three were maintained on previously selected diets, had normal blood sugars at the beginning of therapy and did not show glycosuria before or during the period of treatment with thiouracil. One needed 30 units of protamine zinc insulin daily throughout the period of observation. The others were controlled with diet alone.

All of the remaining eight cases showed improvement in their diabetic status through the use of thiouracil. Six were without glycosuria on diet therapy without insulin but all had high fasting blood sugars when first seen, the actual figures in mg. per 100 cc. being: 350, 280, 207, 201, 194, and 180 respectively. Serial weekly examinations showed a normal blood sugar as soon as the basal metabolic rates were brought within normal levels. The two remaining patients needed insulin to prevent glycosuria. Under treatment with thiouracil the amount of protamine zinc insulin required was reduced from 125 and 30 units respectively to 30 and 10 units respectively.

E. The maintenance dose of thiouracil

Fifty-four patients were followed to complete control of their thyrotoxic state while under treatment with thiouracil. The maintenance doses as related to the initially observed basal metabolic rates are recorded in Table 8. The majority of patients—28 in all—were maintained satisfactorily on 0.2 grams of drug daily. However, the average daily dose for all patients with pretreatment basal metabolic rates of plus 30 or more was slightly higher (0.23 gm.) than that necessary for those whose initial rates were below plus 30 (0.17 gm.). The maintenance dose was determined by "trial and error." In 13 instances the dose had to be increased after gradual reduction, in order to prevent the recurrence of symptoms and signs of thyrotoxicosis: in five instances from 0.1 to 0.2 gm.; in two,

from 0.1 to 0.3 gm.; in four, from 0.2 to 0.3 gm.; and in two, from 0.3 to 0.4 gm. It is therefore patent that cases must be individualized. The drug should not be abandoned as unsatisfactory because too small a maintenance dose is attempted.

F. The discontinuance of therapy

No patient was able to stop treatment until thiouracil had been continued for at least two months. If thiouracil was used less than two months, symptoms invariably returned (Table 2). At the end of two months, it was successfully stopped in five patients. However, attempts to discontinue therapy in some individuals after 15 months have led to an exacerbation of the disease process. Thus far, therefore, there is no "rule of thumb" by which the termination of treatment can be predicted. It is our present practice to reduce the dose of drug at first rapidly until a fairly stable non-toxic state has been attained. Further reduction is made much more gradually, beginning as a rule between the third and fourth months of treatment.

III. DISCUSSION

Williams believes that probably more than 2000 patients with thyrotoxicosis have received thiouracil (61), although his remarks and conclusions are based upon 304 cases sufficiently studied by himself and others to permit satisfactory summation. Since his report was written, *i.e.* since July, 1944, at least 500 additional cases have been discussed in the literature, exclusive of those herein mentioned. It is difficult to make an accurate count as some of the cases have been mentioned by the same author or group of authors in more than one article. Moreover, there are undoubtedly more patients under treatment than have been summarized in the literature, as a number of authors have written only of their unusual experiences, or have only discussed cases bearing on some phase of the action of the drug which they have singled out for special study. It has been our effort to summarize the major clinical data on all our cases so that we may gain perspective on the over-all action of the drug as it may be expected to affect large groups of people when applied in the general practice of medicine. With this in mind certain features in our results justify comment:

A. Toxic reactions

Agranulocytosis occurred in two of our 78 patients (2.5 per cent). These we have described elsewhere in detail (39). This is the only serious complication to be encountered in the use of the drug. It has been reported in seven patients in addition to the two mentioned herein (1, 2, 17, 29, 35, 52, 60). Of these, three have died (17, 29, 35) as a result of the agranulocytic reaction. However, in one of these (29), the patient was 62 years old and was suffering from diabetic coma as well as the drug reaction when admitted to the hospital. Three additional cases have been described in the literature under the title of agranulocytosis in which there was actually only a neutropenia, and the symptoms were mild (34, 35, 44). It is quite likely that most of the patients who have developed an agranulocytosis have been reported not only because of the severity of the symptoms but also because, as is the case with every new drug, the physician's attention is immediately focussed upon any unusual or untoward aspect thereof. If that is the case then there

TABLE 8. DAILY MAINTENANCE DOSE OF THIOURACIL IN RELATION TO THE PRE-TREATMENT BASAL METABOLIC RATE

Initial B.M.R. (% of normal)	No. of patients	Daily dose of thiouracil (gm.)
+50 and over	2	0.4
	8	0.3
	12	0.2
	2	0.1
	Tot. 24	Av. 0.24
+30 to +50	2	0.4
	4	0.3
	10	0.2
	3	0.1
	Tot. 19	Av. 0.23
Up to +30	1	0.3
	6	0.2
	4	0.1
	Tot. 11	Av. 0.17

have been nine reactions in approximately 2500 reported cases, or an incidence of 0.36 per cent. Even if every series ran as high as our own, with an average of 2.5 per cent reactions of a severe nature, the morbidity and mortality is certainly less than that attendant upon previously recognized means for dealing with thyrotoxicosis. The fact remains nevertheless that agranulocytosis is an alarming manifestation of hypersensitivity or toxicity, and should make for caution in the use of the drug by all practioners.

The majority of agranulocytic reactions have occurred between the third and seventh weeks of treatment. A factor in the production of the bone marrow block appears to be the tremendous concentration of the drug in the marrow as shown by Williams, Kay and Jandorf (63). Using human subjects, these workers showed that bone marrow concentrations of thiouracil rose rapidly following the administration of from 0.4 to 1.2 grams of thiouracil daily. Within three days the average bone marrow-blood ratio of the drug was 12, and in those patients treated from six to 22 days the average bone marrow-blood ratio rose to 85. This was the highest concentration of the drug in any tissue of the body. In the patients observed for longer periods of time the thyroid showed the second greatest concentration with a tissue-blood ratio of 46 to 1, that is only slightly more than half that observed for the bone marrow (85 to 1). If possible a successful substitute for thiouracil should have less tendency to pack the bone marrow and even greater proclivity for the thyroid.

One other type of toxic reaction justifies emphasis. We have had two cases in which there occurred chills, fever, and widespread urticarial rashes. Neither in our cases nor in those reported in the literature has this type of untoward response endangered the life of the individual, but in many instances, as in both of our patients, it has been sufficiently severe to warrant cessation of the drug. It appears to be a true hypersensitivity, and has usually occurred before the tenth day of administration of the drug. In many instances, as in both the cases above reported, attempts to reintroduce the drug, even in small quantities, have usually resulted in a reproduction of the symptoms. Desensitization has been attempted by some workers (1–3), but the degree of success is questionable.

B. The uniformity with which all types of thyrotoxicosis may be relieved

If thiouracil is continued a sufficiently long time in sufficiently large dosage it has been our own experience as well as that of the majority of workers that thyrotoxicity whether due to a diffusely hyperplastic or a nodular gland can be completely relieved. In one of our patients (*Case 21*), it was seven weeks before a basal metabolic rate within normal range could be attained, although 0.8 gm. of drug were given for one week, 0.6 gm. for three additional weeks, and 0.4 gms. for the remainder of the seven weeks' period.

Paschkis and his associates also called attention to the necessity for very large doses in one patient who required 2.0 gm. of the drug daily for a short time (46). Rose and McConnell (51) treated one patient for 34 weeks before her basal metabolic rate fell below plus 15 per cent.

As a rule some symptoms are improved as early as the seventh to tenth day, and the average patient is well on the way to complete control by the end of the third week. Some failures have been reported in the literature (22, 49, 51, 57-discussion by Ellis, 59), but in every instance one can say with certainty that the dosage of the drug was too small, the period of trial too short, or previous medication, particularly iodine, not properly evaluated; and so forth. Rose and McConnell (51) have called attention to these factors at some length in discussing their own so-called failures. It seems therefore safe to say that any type of thyrotoxicosis may be relieved by the drug provided proper conditions of treatment are observed.

C. Criteria for optimum treatment

The fact that we have been able to produce the picture of both simple hypothyroidism and myxedema by high dosage of thiouracil in

four patients (*Cases 17, 29, 52,* and *64*) justifies some comment on ways and means of maintaining the patient in an optimal state. Himsworth (22) sharply distinguishes these "true toxic effects" of the drug from the febrile and hematopoietic or "hypersensitive reactions." In avoiding over-dosage, attention to the following have been of value to us:

1. *The basal metabolic rate*

As soon as a basal metabolic rate of plus 15 or below has been attained, we have striven to ascertain immediately the lowest maintenance dose which will keep it between plus 5 and plus 15. It is in this range of basal metabolism that patients have been most consistently free of subjective symptoms, have achieved normal pulse rates and blood pressures, and have established satisfactory increments of weight.

2. *The blood cholesterol*

When a formerly normal or low normal cholesterol rises above the top normal figure (200 mg. per 100 cc.) the dose of drug may be reduced irrespective of the concomitantly recorded basal metabolic rate. Blood cholesterol levels between 175 and 250 mg. per 100 cc. are common in the adequately treated patient.

3. *Enlargement of the thyroid gland*

When enlargement of the thyroid gland occurs, it usually implies the formation of a colloid poor in iodine with a beginning exhaustion of the highly overstimulated thyroid cell. While the decreasing basal metabolic rate and the rising blood cholesterol usually give us warning that this is occurring before the gland actually enlarges, nevertheless there have been several instances in which the enlargement of the gland appeared so rapidly that the other signs had been overlooked. This increase in the thyroid may occur at any time but has usually appeared between the second and sixth months of treatment. Discontinuance of the drug or a reduction in the size of the dose has always been attended by a recession in the thyroid. If on a second occasion cellular exhaustion is produced, the gland responds in a manner similar to that previously observed.

D. The significance of a decrease in the size of the thyroid gland

We have just discussed the probable cause of the enlargement of the thyroid which occurs when treatment with thiouracil is being pushed too far. There remains to be considered the transient decrease in the size of the gland which is most frequently observed between the second and fourth weeks. While we have performed no biopsies, it is our belief that this transient decrease in size corresponds to the time at which the gland is yielding to the tissues the excessive amounts of thyroglobulin present prior to the beginning of treatment. This concept would be in accord with the findings noted in thyroids removed at operation (3, 4, 10, 42, 51, 60).

E. The duration of treatment

Our ability to discontinue the drug in the average patient without a recurrence of symptoms has varied widely . . . from 2.5 to 16 months. This seems to have been the universal experience of all observers. The results of several serve to stress the fact (1–4, 6, 7, 44, 46, 51, 60–62). There is evidence to suggest that the drug can not be successfully discontinued until such time as the thyroid cell has reached an "exhaustion" or "near-exhaustion" stage, or until the excessive hypothalamico-pituitary stimuli have been reduced. Because of the large number of variables implied in the two statements of the above sentence, it is rather obvious that the duration of successful treatment becomes a distinctly individualistic matter.

Unsuccessful attempt has been made on three occasions to stop treatment in one of our patients (*Case 29*) who has been taking thiouracil for 16 months. Abnormal business stresses leading to long hours of work, excessive stimulation with alcohol and coffee, and an initially asthenic constitution seem to be the contributing factors in maintaining his pituitary and thyroid activity at a high level. Another patient of rather mercurial disposition (*Case 41*) has slipped into and out of

hypothyroidism on more than one occasion, although her condition has been continuously watched at not longer than monthly intervals. Therefore, for the present at least, we can not establish a hard-and-fast rule for stopping therapy. This raises the whole problem of how long we should use thiouracil before resorting to some other form of therapy, such as surgery. Our experience affords no scientific answer to this question. Perhaps work of the type already begun by Williams and his associates (63) may throw light upon it. It would certainly be invaluable to know tissue concentrations of the drug after it had been used for months. Do the tissues establish a level varying with the dose of drug used? Can this level be maintained indefinitely without damaging the tissues of the host? The answers to these and similar questions are essential to a full evaluation of the place of thiouracil in the treatment of the thyrotoxic patient.

IV. SUMMARY

1. Ten male and 68 female patients with thyrotoxicosis have been studied while under treatment with thiouracil.

2. Of these 78 patients, 53 had a diffusely hyperplastic and 25, a nodular type of goiter.

3. Periods of treatment have varied from two weeks to 16 months.

4. "Nervousness," apprehension, palpitation, and loss of weight were the most common symptoms and were among the first to disappear.

5. Exophthalmos was present in 38 of the 78 patients, and was decreased under treatment in 17 instances.

6. In 65 instances, the thyroid was initially enlarged. Under treatment there was a transient decrease in size in 20, and a more prolonged increase in size in 21.

7. The auricular fibrillation initially present in 18 individuals disappeared in 12 without other therapy than the thiouracil.

8. Eight of the 78 patients were continued on the drug only sufficiently long to prepare them for surgery.

9. The basal metabolic rate was depressed by thiouracil in both the nodular and hyperplastic types of thyrotoxicosis. The average initial basal metabolic rate for the entire group was plus 46.0 per cent with a low of plus 18 and a high of plus 87. The approximate time taken for the basal metabolic rate to reach plus 15 or below was three weeks.

10. The initial blood cholesterol level was above 200 mg. per 100 cc. in 11 patients. The pretreatment blood level for this substance bore no direct relationship to the height of the basal metabolic rate nor to the severity of the thyrotoxic state. In every instance, as the basal metabolic rate fell, the blood cholesterol rose.

11. Toxic reactions included two cases of agranulocytosis and two cases with severe febrile reactions, chills and urticarial skin lesions.

12. Eleven of the 78 patients had a preexisting diabetes. In three of these 11 patients there was no change in glucose tolerance under treatment.

13. The maintenance dose of thiouracil has varied from 0.1 gm. to 0.4 gm. daily with an average of 0.23 gm. daily for the 67 patients whose initial basal metabolic rates were plus 30 or above.

14. The treatment of 14 patients was successfully discontinued, as follows: at the end of two and a half months in five cases; four months in one; five months in one; six months in two; seven months in two; and eight months in three.

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Thiouracil in the Control of Thyrotoxicosis

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THE rapid accumulation of a relatively large amount of encouraging data pertaining to the therapeutic use of thiouracil suggests that this or some similar compound eventually may attain recognition for the medical treatment of patients with thyrotoxicosis.

The experimental background leading to the development of this form of therapy, as well as the results of its rather extensive clinical trial, have been reviewed by Astwood (1), Williams (14) and others (2, 10, 12, 18). Although the exact scope of the value of thiouracil has not been determined as yet, recent editorial comment (4) intimated that a safe basis seemed to have been established for continued observations concerning its therapeutic action. In conformity with this opinion, the following experiences with the drug are presented.

THE INVESTIGATION

The present report is based upon observations made on 35 unselected thyrotoxic patients who were treated with thiouracil. Nine of these patients were referred to in a previous preliminary communication on the same subject (18). The whole series comprised 30 females and five males ranging in age from 13 to 65 years; the majority, however, were between the ages of 20 and 50 years. On the basis of the clinical diagnoses, there were 19 cases of exophthalmic goiter (Graves' disease), 11 cases of diffuse (non-exophthalmic) toxic goiter and five cases of toxic nodular goiter. Four were examples of recurrent hyperthyroidism following thyroidectomy. One patient was in the sixth month of pregnancy at the time the treatment was started. Another had a thyrotoxic psychosis with extreme agitation. Twenty-five of these patients were under observation in the hospital during the initial stage of their thiouracil therapy; the remainder were followed entirely as out-patients. In the majority of instances, the pre-treatment levels of the basal metabolic rate, the resting pulse rate, the blood chemical constituents, etc., were established by observations on at least two consecutive days. Following the institution of treatment with thiouracil, attention was focussed upon the clinical status of the patient with special reference to any apparent changes in the thyrotoxic manifestations and in the size and consistency of the thyroid gland. Estimations of the B.M.R. and of the concentrations of cholesterol (total) by the method of Myers and Wardell (9) and of the alcohol-insoluble (organic) iodine[1] in the whole blood were performed at weekly intervals and, when possible, leukocyte counts were made twice weekly for the first month. Thereafter, the interval between the tests was lengthened depending upon the therapeutic response or other circumstances.

The initial dosage of thiouracil[2] was 600 milligrams daily given as three doses of 200 milligrams each at approximately six-hourly intervals. With the occurrence of obvious im-

[1] The estimation of iodine in the residue obtained after treating oxalated whole blood with absolute ethyl alcohol was performed by means of a method described by Perkin (11) with certain technical modifications (16, 17).

[2] Supplied by the Lederle Laboratories, Pearl River, New York; courtesy of Dr. Stanton M. Hardy.

provement as indicated by a decline of the B.M.R., usually after one or two weeks, the dose was reduced to 500 or 400 milligrams per day. Subsequent reduction followed until, after four or six weeks, a maintenance dose of 100 milligrams or less per day was established The duration of the treatment of the patients included in this study has been as follows: 12 months or longer, 6 cases; from 9 to 12 months, 2 cases; from 6 to 9 months, 5 cases; from 3 to 6 months, 15 cases; less than 3 months, 7 cases.

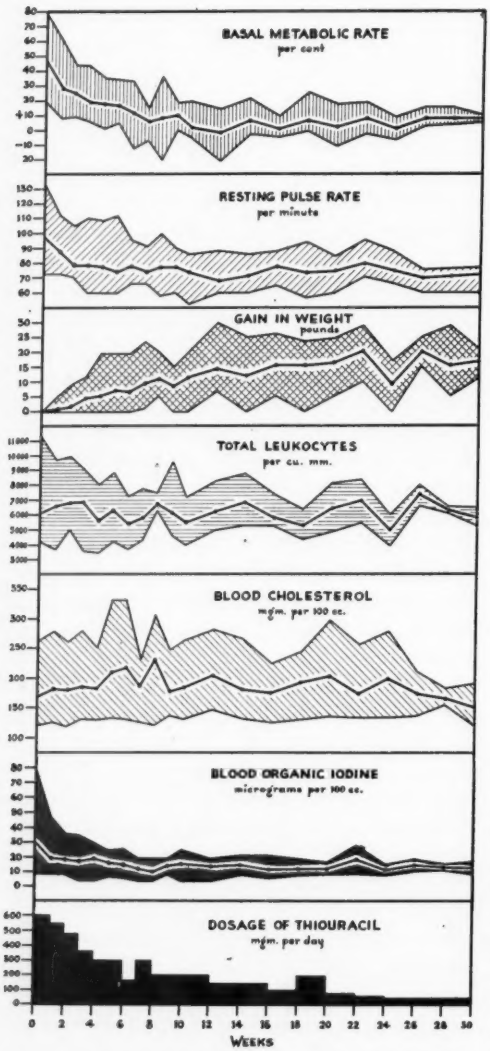

FIG. 1. The effects of thiouracil in the treatment of 30 patients with thyrotoxicosis.

RESULTS

In view of the many variables involved in so-called toxic thyroid disease, a clear-cut picture of the results attainable by any method of treatment is not easy to present.

General Considerations. An improvement of the subjective symptoms is especially difficult to assess quantitatively. However, the relief from the disturbances commonly associated with the hyperthyroid state, such as apprehension, irritability, restlessness, tremor, palpitation, muscular weakness, thermophobia, sweating, vasomotor instability and diarrhoea, is indicative of the usefulness of the drug.

Speaking generally, the results of the treatment with thiouracil in this group of patients may be graded as follows: excellent in 15 cases; good in 10, fairly good in 5 and poor in 5. It is only fair to state that the poor results may have been influenced by certain factors such as failure of cooperation on the part of the patient, lack of adequate data, the previous use of iodine medication and, in one instance, the development of an idiosyncrasy to the drug. On the whole, the response was more satisfactory in the younger patients than in the older ones. Although both the diffusely hyperplastic and the adenomatous goiters responded favorably to the drug, the symptomatic improvement was more striking in the former. The results were highly satisfactory in the cases of post-operative recurrence of hyperthyroidism. The pregnant patient continued to take thiouracil up to and following parturition without apparent ill effect to herself or the child. The psychotic patient regained an essentially normal mentality.

The changes in the objective manifestations of toxic thyroid disease, on the other hand, lend themselves to quantitative appraisal. Included in this category are the basal metabolic rate, the pulse rate, the variations in body weight, the blood cholesterol concentration and the organic iodine

content of the blood. Data pertaining to these features in the 30 responsive cases are shown in Figure 1. The extreme values for the several items at various times up to 30 weeks are depicted along with curves representing the mean values.

The Basal Metabolic Rate. In all the patients but two in the group under consideration, there was a prompt decline of the basal metabolic rate, in some instances to subnormal levels. The length of time required for the B.M.R. to reach +15 per cent or lower varied from two to eight weeks with a general average of about six weeks. There did not appear to be any definite relationship between the degree of thyrotoxicosis and the speed with which the B.M.R. returned to normal. The return was faster, however, in the younger patients than in the elderly ones and delayed in those who had received iodine medication previously. Minor elevations of the B.M.R. during the course of the treatment may have been related in some cases to a too rapid decrease of the dosage of thiouracil.

The Resting Pulse Rate. In every instance the resting pulse rate decreased. Furthermore, in several patients with cardiac irregularity, the rhythm returned to normal either with or without therapy other than the thiouracil.

Gain of Weight. The body weight of 26 of the 30 patients increased during the treatment. The gain of weight was not pronounced during the first two or three weeks, but thereafter the majority of the patients showed a gradual increase in weight and in some cases it became excessive.

The Blood Cholesterol. As has been found by some observers (2, 14), patients who respond to thiouracil may exhibit an increase in the total cholesterol content of the blood sometimes to quite high levels. Such findings have been questioned by others (3). A rise in the cholesterol value occurred in 26 of the patients investigated. No elevation took place in three cases and in one the study was omitted. The rise of the blood cholesterol seemed to correspond, more or less, with the initial drop of the B.M.R. and, in most of the cases, after several weeks the cholesterol concentration tended to level off at an approximately normal figure.

The Blood Organic Iodine. The so-called organic blood iodine is regarded by some investigators as an index of the amount of thyroid hormone produced (15). The normal value for the alcohol-insoluble (organic) iodine estimated by the method employed in this laboratory is from 8 to 12 micrograms per 100 cc. of whole blood. A systematic study of this organic blood iodine was made in 28 of the patients. The pre-treatment values in different cases varied from slightly above normal to 76 μg. per 100 cc. of whole blood. The majority, however, were definitely high, with a general average of 30 μg. The administration of thiouracil brought about a fairly prompt decline of the blood iodine in 21 of the patients, indicating that the amount of thyroid secretion poured into the blood stream was reduced. There was a less pronounced change in seven cases.

The Total Leukocytes. In view of the reputed tendency of thiouracil to cause leukopenia in a relatively small percentage of persons receiving the drug, periodic total leukocyte counts were performed on all 30 patients. In only 6 were counts recorded below 5000 cells per cu. mm. Only 2 of these counts were below 4000 per cu. mm. A reduction of the dosage of thiouracil resulted in a prompt rise of the leukocytes to the normal level.

Gross Changes in the Thyroid Gland. The term "chemical thyroidectomy" as applied by Harrington (5) to the clinical effects of thiouracil is apt in most respects but not, of course, with respect to the ablation of an existing goiter. Regular records of the size of the gland were made in 22 cases in this series by means of measurements of the circumference of the neck. An increase of size was registered in 16 cases and no change was observed in six. Allowing for inaccuracies inherent in this method of estimating changes in the size of the thyroid gland, the observations indicated that in a majority of the cases the gland actually enlarged during thiouracil therapy. The degree of enlargement thus measured, varied from $\frac{1}{4}$ inch to 1 inch, with

an average of $\frac{5}{8}$ inch; an increase which is, perhaps, relatively insignificant considering that a general increase of the body weight occurred also. Two patients elected operation because of the development of pressure symptoms. The glands did, however, tend to become softer and usually the thrill and bruit disappeared. A return to the initial dimensions was noted in several cases during the stage of maintenance treatment.

The Exophthalmos. Of the 19 patients with exophthalmos, a decrease of the proptosis was noted in 12 during the treatment, judged on the basis of inspection only. The degree of exophthalmos was apparently unchanged in 7 cases. It is noteworthy that the regression of this manifestation of the thyrotoxic state succeeded, in some instances by several months, the improvement of the other major symptoms.

Sustained Remissions. It has been claimed by Astwood (1) that the treatment of patients for six to eight months with thiouracil in dosages that maintain a normal or somewhat subnormal basal metabolic rate may initiate spontaneous lasting remissions of the thyrotoxicosis. The administration of thiouracil was stopped, or at least diminished almost to the vanishing point, in six of the patients in the present series after they had been receiving the drug for periods ranging from five to nine months, at which times the thyrotoxic manifestations were in abeyance. In one patient symptoms of thyrotoxicosis and hypermetabolism recurred within two months following the cessation of the treatment. The other patients maintained their remissions, some for as long as six months without the drug. Minor relapses could be induced by physical or emotional stress. Certain patients were reluctant or actually refused to discontinue the use of thiouracil for fear of a recurrence of the thyrotoxic symptoms.

Unresponsiveness. As has been mentioned by Astwood (1), there are two types of patients in particular who do not respond promptly to thiouracil therapy. These are: (1) Those who have been treated with iodine previously and (2) patients with long-standing toxic nodular goiters wherein is stored a large amount of hormone-bearing colloid. Examples of both of these types of cases were encountered in the present series.

In Figure 2 is shown a comparison of the therapeutic response to thiouracil of a patient who had been treated previously with full doses of Lugol's solution and one who had not been so treated. In the former case there was actually a rise of the B.M.R. following the cessation of the iodine medication and during the early stage of thiouracil therapy. The consensus is, however, that if the treatment is persisted, the desired result, as in this case, will follow.

Toxic Reactions. The main disadvantage of thiouracil as a therapeutic agent seems to be its unpredictable tendency to produce toxic reactions of various kinds which, as stated by Williams (14), occur in 10 per cent of cases. The most serious event of this sort is leukopenia and agranulocytosis, an occasional fatality due to the latter condition having been recorded (6, 7). It is noteworthy that in several of the published reports of leukopenia and granulocytopenia associated with the use of thiouracil (8, 13), the dosages were relatively large and sustained. Such complications present a definite handicap to the general therapeutic application of the drug.

One patient in this series responded unfavorably owing to the development of an idiosyncrasy to thiouracil. This was the case of a non-atopic woman, aged 56, with chronic hyperthyroidism. The B.M.R. on two occasions was +41% and +35%. Three days following the institution of treatment with 600 milligrams of thiouracil daily, she complained of headache, insomnia and general malaise. Her apprehension increased, the heart beat became faster and somewhat irregular. There was discomfort in the chest, nausea and occasional vomiting. The temperature gradually rose from normal to 102°F., but there was no sore throat or other evidence of inflammation and no change in the leukocytes. Following cessation of the treatment, the temperature promptly returned to the normal level and the disagreeable symptoms disappeared. Four days later, as a trial, the patient was given 200 milli-

grams of thiouracil as a single dose. Shortly thereafter she experienced a sharp pain in the lumbar region and a pounding sensation in the head. Her face became flushed; the conjunctivae were congested and her eyes burned. There was circumoral pallor. She had a chill and vomited. The temperature rose suddenly to 104.8°F., the pulse rate increased from 80 to 140 per minute and the total leukocytes were 2,400 per cu. mm., 80 per cent of which were neutrophiles. The temperature and the pulse rate dropped almost as rapidly as they had risen and within 24 hours all of the untoward manifestations had disappeared. The total leukocytes had increased to 4,800 per cu. mm. with 70 per cent neutrophiles. Further treatment of this patient with thiouracil has not been attempted.

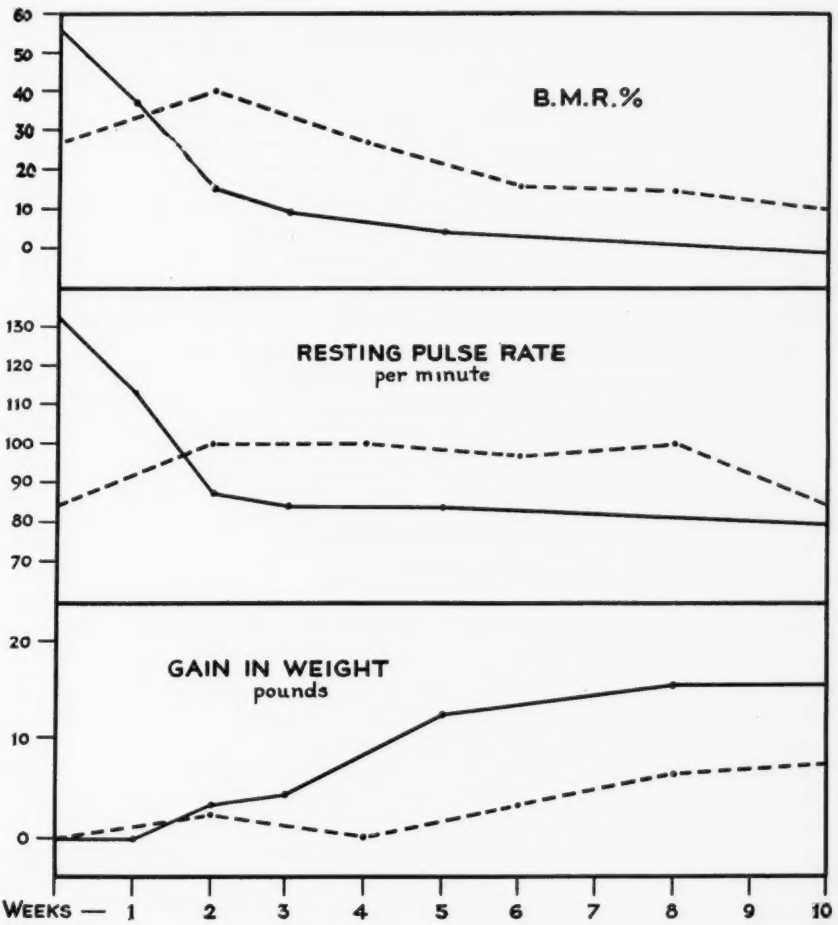

FIG. 2. A comparison of the effects of thiouracil in the treatment of: (1) A thyrotoxic patient who had received no previous iodine medication—*solid lines* and (2) A thyrotoxic patient who had received previous iodine medication—*broken lines*.

SUMMARY

In 30 out of 35 patients with thyrotoxicosis treated with thiouracil for periods of two to 16 months, the results were favorable as indicated by a relief of the thyrotoxic symp-

toms, an increase of body weight and blood cholesterol and a reduction of the organic iodine of the blood. Thiouracil did not alter the size of the thyroid gland or consistently affect the degree of exophthalmos. One patient developed a severe febrile reaction and leukopenia.

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Prolonged Administration of Diethylstilbestrol[1]

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DIETHYLSTILBESTROL in the few years since its introduction has become recognized as a highly effective estrogenic agent for the treatment of a variety of gynecological disorders. In view of the fact that it rather frequently gives rise to nausea or vomiting it was designated by some as "toxic." Despite the failure of several investigations to demonstrate significantly harmful effects of the drug when used within appropriate levels of dosage, its ill repute has persisted.

In December, 1939, we reported our first observations on the so-called toxic effect of diethylstilbestrol. The results of the investigation were published in 1941 (1). These results encouraged us to continue its use and to date we have given diethylstilbestrol to 3227 patients. Varied tests were conducted before, during and following the prolonged administration of diethylstilbestrol. None of these laboratory data yielded evidence to suggest that chronic toxicity or a neoplastic transformation occurs as the result of the therapy. As the evidence accumulated on the relative harmlessness of the drug, we felt justified in deliberately exploring the effects of high dosage of this material. One representative series of studies, of *Case M. M.*, is summarized in Table 1.

Some aspects of the study may be separately considered. There were 86 cases of vulvovaginitis in children of from two to twelve years of age who received from 1.0 to 5.0 mg. of diethylstilbestrol daily. In addition, eight girls, ranging in ages from two to eight years received from 10.0 to 25.0 mg. of diethylstilbestrol daily or every second day for periods of from one to eight months. In this series control tests were made once each month. In addition, roentgenograms of the hands and forearms were made once every 30 or 60 days. In another series of normal children of the same ages, roentgenograms were taken before, during and following the administration of diethylstilbestrol. In this and in the control series no significant changes in ossification were disclosed. In this series the laboratory tests also failed to demonstrate any abnormal conditions.

In a selected cumulative series of 136 women, given diethylstilbestrol for one or another gynecological condition, the dose was gradually increased from 1.0 mg. to 5.0 mg. by mouth every three to seven days until some were taking 100.0 mg. each a day. Furthermore, they were going to the Endocrine Injection Clinic where they received intramuscularly, once or twice weekly, doses of from 25.0 to 250.0 mg. of diethylstilbestrol incorporated in olive oil in a concentration of 25.0 mg. per cc. One third of these patients were started on their diethylstilbestrol in the clinic, where they received smaller doses. They were admitted to the hospital in order that they might be studied more closely, and them large doses were given. This group demonstrated that, regardless of the amounts administered, there was no obvious harm to the patients. They were then dismissed to the clinic where they were continued on the doses of 100 mg. per day with additional intramuscular injections of from 50 to 100

[1] Permission to do this research granted by the Research Committee of the Jefferson Davis Hospital.

mg. two to six times weekly. A complete blood count and a urine analysis were performed two to three times weekly. In none of these cases was it possible to demonstrate by these tests any abnormal findings resulting from diethylstilbestrol therapy.

One woman, aged 38, died as the result of an auto accident while she was taking daily treatment of 5.0 milligrams of diethylstilbestrol; she had received a total of 250 milligrams. The pathologists were unable to discover any sign of gross or microscopic evidence of damage to the liver or to any other organ of the body as the result of the stilbestrol therapy.

Two patients, each about three months pregnant, were under observation because of threatened abortion. Each patient was given 950.0 milligrams of diethylstilbestrol weekly for an average period of 19 weeks, a total of 18,000 milligrams of diethylstilbestrol. During the latter part of the fifth month both mothers aborted live babies. Both babies died within several days. Each baby was autopsied. The parenchymatous organs were carefully studied grossly and microscopically, and the pathologists could demonstrate no significant changes from the normal.

A third series of studies were carried out on thirty-one normally pregnant women. Each received 100.0 milligrams of diethylstilbestrol daily, from the third month of pregnancy to term, a total of 18,000 milligrams for each. The 31 babies born were normal. All the babies exhibited a darkening of the areolae around their nipples, labia, and linea alba, similar in intensity to that of their mothers, indicating that this effect of diethylstilbestrol also is shared by the fetus. The diethylstilbestrol in daily doses of 100.0 milligrams did

TABLE 1. PROTOCOL OF TESTS MADE ON *M.M.*, A negro girl, fourteen years of age. The study began July 9, 1939. The patient had profuse hemorrhage when first seen.
Amount of diethylstilbestrol administered (mg. per dose)

Month	Consecutive weeks	Orally	Intramuscularly	Total dose	Data
1	1	8.0	80.0	88.0	First menses in her life began as profuse flooding.
	2	11.5	6.0	17.5	This episode of flooding stopped after 75 mg. had
	3	17.5	2.0	19.5	been given.
	4	18.5		18.5	
				143.5	
2	5	7.0	7.0	14.0	
	6	7.0	7.0	14.0	
	7	8.5	8.5	17.0	
	8	17.5	17.5	35.0	
				80.0	
3	9	20.0	20.0	40.0	Six days of bleeding.
	10	65.0	65.0	120.0	Spotted 6 days this week.
	11	70.0	70.0	140.0	
	12	55.0	55.0	110.0	Seven days bleeding.
				410.0	
4	13	55.0	80.0	135.0	Spotted on 7th day.
	14	35.0	35.0	70.0	Spotted on 6th and 7th days.
	15	35.0	35.0	70.0	
	16	35.0	35.0	70.0	
				345.0	
5	17	35.0		35.0	Spotted past 3 days.
	18	35.0		35.0	
	19	35.0		35.0	
	20	35.0		35.0	
				140.0	

TABLE 1.—*Continued*

Month	Consecutive weeks	Orally	Intramuscularly	Total dose	Data
6	21	35.0		35.0	
	22	35.0		35.0	Bled first 6 days.
	23	35.0		35.0	
	24	35.0		35.0	
				140.0	
7	25	50.0		50.0	
	26	40.0		40.0	
	27	45.0		45.0	Spotted last 4 days.
	28	70.0		70.0	
				205.0	
8	29	70.0		70.0	
	30	85.0		85.0	
	31	105.0		105.0	
	32	105.0		105.0	
				365.0	
9	33	105.0		105.0	Menstrual flow normal 4 days.
	34	105.0		105.0	
	35	105.0		105.0	
	36	105.0		105.0	
				420.0	
10	37	105.0		105.0	
	38	105.0		105.0	
	39	105.0		105.0	
	40	105.0		105.0	No flow this month.
				420.0	
11	41	105.0		105.0	
	42	105.0		105.0	
	43	105.0		105.0	
	44	105.0		105.0	No flow.
				420.0	
12	45	315.0		315.0	No nausea or vomiting.
	46	700.0		700.0	No flow in 3 months.
	47	700.0		700.0	Has attack of lower abdominal pain.
	48	700.0		700.0	No nausea or vomiting in 2 months.
				2,415.0	
13	49	700.0		700.0	
	50	700.0		700.0	
	51	700.0	200.0	900.0	
	52	700.0		700.0	No flow.
				3,000.0	
14	53	700.0	1,250.0	1,950.0	
	54	700.0	3,500.0	4,200.0	
	55	700.0	500.0	1,200.0	
	56	700.0		700.0	No flow.
				8,050.0	
15	57	400.0	1,000.0	1,400.0	

Study ended Sept. 5, 1940.
The patient had 17,783.5 mg. stilbestrol without significant changes in the laboratory findings.

Laboratory findings of Case M.M.

Blood examinations:

Date	Hb % (T)	R.B.C.	W.B.C.	Neut. %	Lymph. %	Eo. %	Mono. %
7-20-39	50	2.9	6.7	66	30	1	3
8- 3-39	59	3.5	5.4	66	34		
8-22-39	58	2.9	5.2	74	26		
9-13-39	66	3.4	10.2	78	18	3	1
10-11-39	70	3.8	7.7	68	20	3	9
10-21-39	84	4.0	7.8	65	35		
11- 5-39	66	3.6	8.2	72	23	4	1
12-23-39	68	3.3	7.0	58	36	2	4
1- 6-40	72	4.0	9.4	80	16	2	2
2-17-40	64	3.3	6.7	69	28	1	2
3- 2-40	62	3.2	6.8	64	34	2	
3-30-40	79	3.9	6.2	77	20	3	
4-13-40	77	3.5	6.2	64	46	6	3
5- 4-40	67	3.6	6.5	45	30	2	4
6- 1-40	82	3.6	5.4	60	36	2	2
6-29-40	68	4.1	6.4	62	36	2	
7-29-40	71	3.4	9.2	78	18	2	2
7-31-40	71	3.7	15.0	72	22	2	2
8- 2-40	77	3.7	9.9	74	26	2	
8-12-40	66	3.6	9.0	63	34	1	2
8-26-40	71	3.9	8.5	70	26	2	2
8-31-40	73	4.2	6.6	69	28	2	1
9-11-40	81	3.9	8.6	71	27		2
9-14-40			6.8	68	29		3

Urine examinations:

Date	How obtained	Findings
7-22-39	Catheter	Normal
11-15-39	Catheter	1–5 w.b.c. per h.p.f.
6- 1-40	Voided	1–5 w.b.c. per h.p.f.
7-29-40	Voided	5–8 w.b.c. per h.p.f. Tr. of albumin.
7-31-40	Voided	150–200 w.b.c. per h.p.f. Tr. of albumin
8-31-40	Voided	Normal

Blood serum creatinine values (mg. per 100 cc.)

Date	Result
6-29-40	1.5
7-15-40	1.4

Sedimentation rate mm. per hour

Date	Result
8- 9-30	18.5
8-22-39	25.0
9-13-39	26.0
10-11-39	12.0
10-21-39	22.0
12- 9-39	13.0
12-23-39	20.0
1-27-40	30.0
2-17-40	28.0
3- 2-40	20.0
3-30-40	24.5
4-13-40	24.0
5- 4-40	19.0
7-15-40	31.5
7-29-40	34.0
8-12-40	35.0
8-26-40	24.0
9-11-40	20.0

Blood serum sodium chloride values, mg.%

Date	Result
8-22-39	485
1- 6-40	492
1-27-40	487
3- 2-40	430
2-17-40	495
3-30-40	472
6-29-40	491
7-15-40	467
7-29-40	475
8-12-40	462
8-26-40	515
9-11-40	484

Serum non-protein nitrogen values (mg. per 100 cc.)

Date	Result
10-14-39	36.7
10-21-39	28.0
1- 6-40	26.8
1-27-40	30.0
2-17-40	23.8
3- 2-40	31.8
3-30-40	30.0
6- 1 40	34.4
6 29-40	34.6
7-15-40	33.0
7-29-40	23.0
8-12-40	29.0
8-26-40	21.6
9-11-40	31.0

Blood serum glucose values (mg.%)

Date	Result
3-30-40	84.7
4-13-40	89.3
5- 4-40	85.8
6-29-40	111.7
7-15-40	80.0
7-29-40	79.7
8-12-40	68.7
8-26-40	69.2
9-11-40	75.2

Blood serum cholesterol values (mg.%)

Date	Result
11-17-39	200
4-15-40	236
5- 4-40	271
7-15-40	255
7-29-40	171
8-13-40	173
8-27-40	188
9-13-40	210

Icterus index:

Date	Result
12-23-39	4
1- 6-40	4
1-27-40	4
2-17-40	3
3- 2-40	3
7-15-40	3
7-29-40	3
3-30-40	7
8-13-40	4
8-27-40	5
9-13-40	5

Endometrial biopsy report:

11-15-39 Endometrium in resting stage with marked dilatation of glands.

Serology:

Date	Report	
11-17-39	Kolmer negative	Kline negative
12-28-39	Kolmer anticomplementary	Kline negative
6- 1-40	Kolmer negative	Kline negative

Roentgen examinations:

Date	Report
1-25-40	Epiphyses show no change.
7-10-40	Hands and forearms normal for bone conditions.
8-21-40	Long bones show no changes attributable to diethylstilbestrol.
2-19-44	This patient is near term. Her obstetrical history and physical findings have been normal throughout the pregnancy.
3-13-44	Normal male infant delivered.

Findings on M.M. after delivery

Date	Hb%	R.B.C.	W.B.C.	Neut.	Lymph.	Eo.	Mono.	Sed. rate
5- 4-44	68	3.6	4.4	51	42	5	2	27.0 mm.
5-20-44	60	3.6	5.5	61	39			18.0 mm.
7-31-44	64	3.3	6.0	48	49	1	2	24.0 mm.
9-23-44	80	4.1	5.1	52	39	5	4	18.0 mm.

Urine findings

Date	How obtained	Sugar	Albumin	Epith.	W.B.C.
9-30-44	voided	None	Trace	pos. 1	50–60
10-14-44	voided	None	None	pos. 3	None

Vaginal smears

Date	Epi.	Pus.	Mono.	Tri.	G.C.	Staph.	Strep.	B. coli	pH
4-26-44	None	None	None	None	None	Pos. 3	None	Pos. 2	6.0
8-19-44	Blood Wassermann: negative.								

Tissue Examinations

Date	Tissue	Findings
4-26-44	Endometrial	Resting—6 weeks post-partum
4-27-44	Culture for Monilia: negative.	
5- 1-44	Endometrial	Late proliferative

not provoke any of the usual unfavorable effects in these pregnant patients.

Ten of these patients were each given 500 milligrams as a single intramuscular dose. All became nauseated and vomited just as do non-pregnant women. It requires 500 milligrams or more of diethylstilbestrol in a single dose to produce the same nausea and vomiting in a pregnant woman that from 0.75 to 5.0 milligrams produces in the non-pregnant woman. In brief, the pregnant woman tolerates with ease 1000 times the dosage of diethylstilbestrol required to produce side effects in a non-pregnant woman. The liver in pregnancy can metabolize apparently up to 500 milligrams per day, and only 0.5 milligrams per day in the non-pregnant woman.

Teague, of New Orleans, (2) studying the toxicity of diethylstilbestrol in rats, calculated that it would require on the basis of body weight, about 7000 milligrams of diethylstilbestrol per day for 30 days to harm an average sized woman.

Other than the nausea and vomiting, which appears in from four to six hours after taking a 0.75 to 5.0 milligram uncoated tablet of diethylstilbestrol, there was no "toxicity" demonstrable. Neither skin rash nor marked edema of the labia has been observed in any of our cases. A slight amount of edema of the labia has been seen, however. The nausea and vomiting passes away in from four to six days if the drug is continued. It has been observed that there is no quanitative relationship of the nausea or vomiting in a non-pregnant patient, whether 5.0 or 250.0 milligrams is ad-

TABLE 2. COMPOSITION OF A SERIES OF 426 CASES OF GYNECIC DISORDERS AND AVERAGE TOTAL DOSAGE OF DIETHYLSTILBESTROL IN EACH CATEGORY.

Condition	Number of Cases	Average total dosage (mg.)
Menometrorrhagia	221	115
Amenorrhea	20	40
Loss of libido	6	200
Hypoplastic uterus	1	40
Dysmenorrhea	27	15
Senile vaginitis	9	14
Sterility	1	100
Vulvovaginitis	5	40
Oligomenorrhea	6	40
Hypomenorrhea	19	40
Menopause	46	40
Painful breast	4	100
Acne of face	1	40
Hypoplasia of breast	1	80
Ovarian cysts	6	100
Ill feeling at menses	5	40
Menses research	25	800
Miscellaneous cases	23	500
	426	

In this series of cases 2,057 laboratory determinations of various sorts were made. For the detection of any possible toxic influences blood sedimentation rates and complete blood counts were principally relied upon.

ministered at a single dose and every day thereafter for 30 days. Obviously these side effects do cause some nutritional imbalance, which is only transient however.

The only untoward effect observed was uterine bleeding which was seen in cases with an intact uterus and a patent cervix, and which were given 1.0 milligram (25,000 international units) of diethylstilbestrol daily for more than 25 consecutive days. This will occur in the normally menstruating woman. The production of uterine bleeding in the menopausal patient is quite alarming sometimes. No woman with an intact uterus should be given 1.0 milligram of diethylstilbestrol daily for a period of 30 or more days. This is especially true in the menopausal patient.

Further details are summarized in tables 1 and 2.

CONCLUSION

From an extensive series of observations in women given massive doses of diethylstilbestrol, one may conclude that there is no demonstrable evidence to indicate that harmful changes result from such massive therapy.

Diethylstilbestrol is a non-toxic drug when the doses recommended in the literature are followed.

This drug, in the pregnant woman, produces no nausea until a dose of 500.0 milligrams per day is given. It is suggested that the increase in liver metabolism permits these increased dosages.

Diethylstilbestrol may be used without fear of serious consequence. It is a valuable drug.

The laboratory work as reported herein was carried out in the Jefferson Davis Hospital laboratories under the supervision of Dr. Donald G. Henderson, Dr. Peter Marcuse and Dr. W. W. Coulter, our pathologists, and to D. Clair E. Folsome, I wish to express my appreciation.

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EDITORIAL

THE PRESENT NUMBER of the Journal marks the initiation of a new Section on "Methods and Technics." Its purpose is to provide space for the regular publication of special methods and technical procedures pertinent to the clinical investigation of endocrine functions. The Journal has in the past welcomed such communications, but the Editorial Board has recognized that numerous technical procedures of merit being utilized in laboratories throughout the country have not reached the pages of the Journal for various reasons. Thus, they may, for example, not appear to the originator to merit formal publication since they may represent modifications of existing methods. Nevertheless, such modifications which serve to simplify or increase the accuracy of any procedure, deserve a more widespread circulation.

It is axiomatic that the development of any field of clinical investigation is, to a large extent, dependent upon the existence of reliable objective criteria for its study. It is hoped that the institution of this new Section will encourage laboratories to make brief communications relating to original procedures and to modifications of existing methods; and that it will thus serve to accelerate a wider use of reliable methods, and lead to a better standardization of procedures already in common use.

METHODS AND TECHNIQUES

A Rapid Method for Demucification and Staining of Seminal Smears

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DETERMINATION of the incidence of various morphologic types of spermatozoa in the ejaculate is of value in establishing levels of fertility in the male (2–5). In order to insure satisfactory and routine clinical application, a method must be rapid, must eliminate artifacts and must permit delineation of all the cellular elements present in the ejaculate. To be of real practical value, moreover, a method should give consistent results which are readily reproducible by the same observer or by other workers. A serious handicap in attaining all these objectives is the presence of extra-cellular debris and mucus which interfere with interpretations of cell morphology. The present report describes a procedure which combines demucification with extremely rapid killing and fixation. This method employs a staining technic previously described by workers in our laboratory (1).

PROCEDURE

Thin or thick smears are prepared in the usual manner after spontaneous liquefaction of the ejaculate has been established. Since the cells of some specimens have a tendency to clump after two hours, it has been found best not to delay making smears beyond this time.

Killing and Fixation

The smears are placed immediately in a 1:1 mixture of absolute alcohol and ether for 30 seconds. This insures rapid fixation, which assures that all the cells will be retained on the slide and will stain homogeneously.

Dehydration

1. Wash in 50% alcohol, 1 to 2 seconds.
2. Wash in distilled water, 1 to 2 seconds.

Demucification

1. Place in acidified water (8 drops concentrated HCl to 40 cc. distilled water) until the slide is no longer opaque. This usually requires 1 to 2 minutes.
2. Wash in distilled water, 1 to 2 seconds.

Staining

1. Stain with eosin (Eosin Y 1% aqueous solution), 30 seconds.
2. Wash in 50% alcohol, 1 to 2 seconds.
3. Stain in Harris' hematoxylin, 1 minute.
4. Wash in tap water, 1 to 2 seconds.
5. Stain in fast green (F. C. F. 0.5% aqueous solution), 1 second.
6. Wash in 95% alcohol, 1 to 2 seconds.
7. Wash rapidly in absolute alcohol, 1 to 2 seconds until slide appears clear of stain.
8. Clear in xylol, 3 minutes.
9. Cover with Clarite.

[1] The expenses for these studies in part were defrayed by a grant from the National Committee on Maternal Health.

RESULTS

The entire procedure requires about 9 minutes. Rapid killing and fixation permits retention on the slide of all the cellular elements of the ejaculate and prevents distortion which occurs with slow drying of the cells or fixation by heat. All the cells take the stain readily. The various components of the ejaculate are stained differentially as follows:

Mature spermatozoa		Developmental forms (*Spermatocytes* and *Spermatids*)	
Nucleus	pink	*Nucleus*	purple
Acrosome	blue	*Cytoplasm*	blue
Body	green		green
Tail	green		

Other Components

Cytoplasmic fragments attached to certain immature cells	green
Leucocytes (nuclei)	purplish to dark blue
Large squamous epithelial cells of urethral origin	deep pink or green

SUMMARY

A method of preparing seminal smears for morphologic study is described which combines rapid killing and fixation of cells with effective demucification. This procedure possesses the three-fold advantages of minimizing distortion, eliminating cell loss from the slide, and facilitating staining of all the cellular elements in the ejaculate.

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Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* F. A. DE LA BALZE, ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNA FORBES, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REFORZO-MEMBRIVES, A. E. MEYER, DORIS PHELPS, E. C. REIFENSTEIN, JR., RUTH ST. JOHN, HAROLD WOOSTER, AND J. ZANARTU.

GONADS

ABARBANEL, A. R.

The spasmolysant action of magnesium ions on the tetanically contracting human gravid uterus. *Am. J. Obst. and Gynec. 49:* 473 (1945).

The magnesium ion has immediate spasmolysant effects upon the tetanically contracting human gravid uterus. Magnesium will abolish tetany induced by posterior pituitary hormone, including pitressin, pitocin and pituitrin, quinine, ergonovene and methergine. The magnesium ion has no demonstrable effect upon the pattern of uterine motility in the first stage of labor but the author states it does have a definite analgesic effect. The clinical applications are discussed.—*C.D.D.*

ABEL, S.

Androgenic therapy in malignant disease of the female genitalia: preliminary report. *Am. J. Obst. and Gynec. 49:* 327 (1945).

Five patients with previously treated but progressively advancing malignancies of the uterine corpus and cervix were given testosterone propionate intramuscularly in arbitrary dosage of 140 to 150 mg. weekly. These patients have been treated for 10 months. Feeling of well-being, improved morale, control of menopausal symptoms and increased libido have been observed. To date, there is nothing to indicate any regression or retardation of the malignant process. With the dosage used, masculinization, including hypertrophy of the clitoris, development of a beard and voice change, has appeared in all 5 patients. Acneform eruptions have occurred in three. Vaginal smears have tended towards the atrophic state and have changed little during treatment. In one of these patients, metastatic lesions progressed during the course of treatment.—*C.D.D.*

KLOPP, C., N. F. YOUNG, AND H. C. TAYLOR, JR.

The effects of testosterone and of testosterone propionate on renal functions in man. *J. Clin. Invest. 24:* 189 (1945).

In four normal adult males, one eunuchoid male and four individuals with "disorders commonly associated with renal insufficiency," several functions of the kidney were studied before and after the administration of testosterone and testosterone propionate administered intramuscularly in daily doses of 90 to 300 mg. for periods varying from 8 to 29 days. The rate of glomerular filtration was measured by the clearance of mannitol. Renal blood flow was determined from the plasma clearance of sodium-p-hippurate while plasma concentrations were maintained between 1.0 and 3.1 mg. per 100 cc. Tubular excretory mass was indicated by the clearance of sodium-p-hippurate when the plasma concentration of that compound was kept above 66.5 mg. per 100 cc. The maximal rate of tubular reabsorption of glucose was measured at plasma glucose concentrations above 350 mg. per 100 cc. The administered hormones were without measurable effect upon the functional capacity of the kidney under the conditions above noted.—*T.H.McG.*

MURPHY, D. P.

The role of the intermittent contractions of the uterus in the process of labor. *Am. J. Obst. & Gynec. 49:* 186 (1945).

Among the tracings of the uterine activity secured from some 1,800 patients when in labor, two individuals had records with no intermittent contractions. These observations were all made with the Lorand tocograph. In view of these findings, the author believes that any efforts to be expended in initiating labor, or in improving labors of poor quality, should be directed primarily at some more fundamental purpose than in merely trying to influence the

power of the uterus to contract intermittently. —*C.D.D.*

STRASSMANN, E. O.

Development and degeneration of ovum and follicle as observed by intravital staining. *Am. J. Obst. & Gynec. 49:* 343 (1945).

Intravital staining of cat ovaries was carried out by the intravenous injection of indigo carmine and trypan blue. Intact ova and granulosa cells do not take the stain. It is a sign of cellular death or degeneration if the dye appears within the nucleus or the cytoplasm. Intravital staining indicates the beginning degeneration of the ovum at a time when no change of structure is visible. This demonstrates that degeneration of any follicle begins in the nucleus of the ovum, progressing further to the ooplasm and finally to the granulosa cells. The zona pellucida of the intact ova takes intravital dyes and intimate connections between the zona and the interspaces between the granulosa cells are seen. No connection between the ovum proper and the zona was visualized. This makes it probable that the zona is deposited from the outside to the ovum. The author believes the liquor folliculi depends closely upon the activities of the circulation of blood and lymph for its origin, that it is possibly modified by the influence of the granulosa cells but definitely not by their liquefaction. The author points out several problems to which an intravital staining technique may be applied.—*C.D.D.*

PANCREAS

VON BAKAY, L., JR.

Regeneration of islands of Langerhans. *Virchows Arch. f. path. Anat., 310:* 291 (1943).

Microscopic studies of thirty specimens from adults showed that postnatal island regeneration occurs under pathological conditions in cases with impairment of the entire pancreas, i.e., in cases of true diabetes, chronic pancreatitis, and pancreatic cirrhosis, or in cases in which the functional disturbance results from circulatory insufficiency (arteriosclerosis of the pancreas). The absence of any clinical symptoms of diabetes may be explained by the compensating effect of an intensive regenerative process in the islands of Langerhans. In addition to the hypertrophy of epithelium in the excretory ducts, the increase in the insular system is due to the transformation of the acini and to the segmentation of the old islands. Traces of this regeneration could be found in almost any case of diabetes. From three to four new islands are sometimes present adjacent to the proliferating excretory ducts. The regenerative tendency is suggested by the fact that in addition to the large hydropic islands, others may be found which consist of small, dense, dark-colored cells. They are surrounded by a ring of connective tissue which is thicker than that found in normal cases. Vessels are not found within these islands. Their rudimentary character explains the absence of clinical improvement in spite of the regenerative process which was demonstrated on microscopic examination. Regeneration in the head of the pancreas in a patient aged sixty-five suggested that the regenerative capacity is not reduced with advanced age.—*Courtesy Diabetes Abstracts.*

BALLANTYNE, A. J.

Retinal changes associated with diabetes and with hypertension. A comparison and contrast. *Arch. Ophthalmol. 33:* 97 (1945).

The retinopathies of diabetes and of the hypertensive diseases are separate entities both clinically and histologically. In both conditions the earliest recognizable lesions are pathological changes in the retinal vessels. In diabetes these affect primarily the venous, in hypertension the arterial side of the retinal circulation. In diabetes these changes point to a venous stasis and, in addition to the familiar hemorrhages and exudates, include congestion of the veins, microaneurysms on the capillaries and gross changes in the principal veins. Microaneurysms may occur alone and seem to be the earliest recognizable change in the diabetic fundus. Occurring at the posterior pole of the fundus, alone or with a few punctate exudates, they are of great diagnostic significance. The microaneurysms are found on the capillaries which pass through the inner nuclear layer to link the superficial and deep retinal plexuses. The most striking changes in the larger retinal veins of the diabetic appear as expansions, beading, and the formation of loops, coils and networks, and the predominant histological changes at this stage are phlebosclerosis and intra- and preretinal networks of large thin-walled vessels. The hemorrhages in diabetic retinopathy occur primarily in the central area of the fundus, are characteristically of rounded form, and are found chiefly in the deep layers, for the most

part the internuclear. In hypertension arterial changes predominate, the hemorrhages are primarily circumpapillary and striate in appearance, owing to their situation in the nerve fiber layer. Exudates are found in the deep layers, but also include patches of ganglioform degeneration in the nerve fiber layer. It is suggested that in both forms of retinopathy toxic factors are responsible for the initial vessel changes.—*Author's Summary.*

BARACH, J. H.

Normal standards in the treatment of young persons with diabetes. *Am. J. Dis. Child. 69:* 92 (1945).

After a review of present day standards of age-height-weight values, charts based on averages obtained from a large number of measurements are constructed. These charts portray the normal trends of growth from the ages of 1 to 21 years. On the basis of the generally accepted values for caloric requirement per day and daily protein requirement per kg. of body weight by growing children and of the amounts considered normal and adequate for children of various ages, a table of diets was constructed to serve as a standard for this study. The growth curves of 135 children with diabetes who had been under observation for 2 to 12 years were superimposed on the normal growth charts, and this revealed that some of the children were of normal size, others were below normal and the remainder were oversize. The caloric values of the diets on which these children had been subsisting were compared with those of normal or adequate diets, and it was found that some children attained normal growth on diets of lesser caloric value than ordinarily prescribed and others did not exceed normal growth regardless of the fact that they had been given diets of greater value than considered necessary for normal growth. The generously fed children required from 1.5 to nearly 2 times as much insulin as those who had been subsisting on conservative diets.—*Author's Summary.*

BLACK, D. R.

Experimental diabetes. *J. Missouri M. A. 41:* 231 (1944).

The discussion follows lines that help in everyday treatment, considering, first, the relation of various endocrine glands to diabetes; second, arteriosclerosis and capillary friability; and, third, diagnosis of the disease, with a discussion of the significance of glycosuria. After consideration of the various extrapancreatic influences on the pathogenesis and course of diabetes, the fact still remains that the only therapeutic approach to control of the disease at present is one of diet and proper insulin dosage. Heretofore, the renal threshold has been described as the blood-sugar level at which sugar appears in the urine. This point would vary, of course, with the rise or fall of the blood sugar. In the light of present explanation, the renal threshold may be defined as that concentration of blood sugar at which the quantity entering the tubules per minute exceeds that which the tubules can reabsorb in the same interval. It is therefore apparent from Mirsky's report that the concentration of sugar in the urine is not in itself an accurate index of the severity of diabetes.—*Courtesy Diabetes Abstracts.*